DESCRIPTION

ORNITHINE DERIVATIVES AS PROSTAGLANDIN E_2 AGONISTS OR ANTAGONISTS

TECHNICAL FIELD

This invention relates to new ornithine derivatives and pharmaceutically acceptable salts thereof which are useful as prostaglandin E_2 (hereinafter described as PGE_2) agonist or antagonist.

BACKGROUND ART

PGE_2 is known as one of the metabolites in an arachidonate cascade. It is also known that PGE_2 has various activities such as pain inducing activity, pro- or anti-inflammatory activity, uterine contractile activity, a promoting effect on digestive peristalsis, an awaking activity, a suppressive effect on gastric acid secretion, hypotensive activity, platelet inhibition activity, bone-resorbing activity, angiogenic activity, or the like.

PGE_2-sensitive receptors have been sub-divided into four subtypes, EP1, EP2, EP3 and EP4, and these receptors have a wide distribution in various tissues. The effects associated with EP1 receptor activator are believed to be mediated by mobilization of Ca^{2+} from intracellular stores. The EP3 receptor is an example of promiscuous receptor that may couple to different second-messenger systems. Further, the effects associated with EP2 and EP4 receptors activator may be considered as inhibitory, and are believed to be associated with a stimulation of adenylate cyclase and an increase in levels of intracellular cyclic AMP. Especially, EP4 receptor may be considered to be associated with smooth muscle relaxation,

anti-inflammatory or pro-inflammatory activities, lymphocyte differentiation, antiallergic activities, kidney dysfunction, mesangial cell relaxation or proliferation, gastric or enteric mucus secretion, or the like.

PGE_2 receptor blockers, in other words "PGE_2 antagonists", possess binding activities to PGE_2-sensitive receptors. Accordingly, they possess a PGE_2-antagonizing or PGE_2-inhibiting activity. Therefore, they are expected as a medicament to treat and prevent PGE_2 mediated diseases. Similarly, PGE_2 agonists can be medicaments for PGE_2 mediated diseases. These PGE_2 agonists or antagonists are expected as a medicament to treat and prevent EP4 receptors-mediated diseases, such as kidney dysfunction, inflammatory conditions, various pains, or the like in human beings or animals.

Such PGE_2 antagonist is known. For example, in WO 00/16760 and WO 00/18744, oxazole compounds are disclosed.

DISCLOSURE OF INVENTION

Under the above situation, the inventors of the present invention found that the compounds having an ornithine skeleton or ornithine derivative skeleton bind preferentially to PGE_2 receptor, therefore they can be good PGE_2 agonists or antagonists, particularly EP4 receptor blockers. As the result, the inventors completed this invention.

Accordingly, the present invention relates to novel ornithine derivatives which are useful for treating or preventing PGE_2 mediated diseases. One object of this invention is to provide new compound and pharmaceutically acceptable salt thereof as prostaglandin E_2 agonists or antagonists.

Another object of this invention is to provide a medicament and pharmaceutical composition containing the compound as an active ingredient.

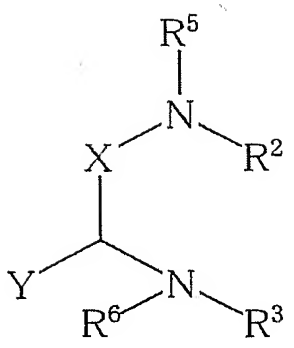
A further object of this invention is to provide an agonist or antagonist of PGE_2 consisting of the ornithine derivative and a method for treatment and/or prevention of PGE_2 mediated diseases which comprises administering an effective amount of the ornithine derivative.

A further object of the present invention is to provide a use of the ornithine derivative.

A further object of the present invention is to provide the compound and pharmaceutically acceptable salt thereof which are useful for the manufacture of medicaments for treating or preventing conditions mediated by PGE_2, more particularly useful for treating or preventing kidney dysfunction, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, allergic disease, cancer and neurodegenerative diseases.

A further object of this invention is to provide the commercial package comprising the pharmaceutical composition containing the ornithine derivative.

The ornithine derivative of this invention can be represented by the following formula (I):



(I)

wherein
X is -CO- or $-(CH_2)_k-$ (wherein k is 1, 2 or 3);

Y is
(1) lower alkyl, or
(2) $Z-(CH_2)_n-$,
{wherein
Z is
(1) aryl, or
(2) $R^1-CO-NR^4-$
(wherein
R^1 is (1) aryl, heterocyclyl,
aryl-(lower alkyl),
aryl-(lower alkoxy), or
heterocyclyl-(lower alkoxy),
each of which may be substituted
with one or more substituent(s)
selected from the group
consisting of
(a) lower alkyl,
(b) halogen and
(c) hydroxy; or
(2) lower alkoxy; and
R^4 is hydrogen, or lower alkyl); and
n is 1, 2, 3, 4, 5 or 6};

R^2 is (1) lower alkyl, aryl-(lower alkyl) or (lower alkyl)thio-(lower alkyl), each of which may be substituted with one or more substituent(s) selected from the group consisting of
(a) heterocyclyl,
(b) carboxy,
(c) carboxy-(lower alkyl),
(d) amidated carboxy,
(e) (lower alkoxy)carbonyl which may be substituted with cycloalkyl, heterocyclyl or (lower alkanoyl)oxy; and
(f) cyano; or
(2) aryl which may be substituted with lower alkyl, lower alkenyl, aryl, lower alkoxy, (lower alkyl)amino, (lower alkyl)thio, carboxy, (lower alkoxy)carbonyl, (lower alkoxy)-(lower alkyl), (lower alkyl)amino-(lower alkyl), or (lower alkyl)thio-(lower alkyl), each of which may be further substituted with one or more substituent(s) selected from the group consisting of
(a) heterocyclyl,
(b) (lower alkoxy)carbonyl,
(c) carboxy and
(d) amidated carboxy;

R^3 is (1) $-Q-R^7$,
[wherein
Q is $-CO-$ or $-SO_2-$,
R^7 is (a) lower alkyl which may be substituted with

one or more substituent(s) selected from the group consisting of
cycloalkyl,
aryl which may be further substituted with aryl(s), and
heterocyclyl,
(b) lower alkenyl which may be substituted with one or more substituent(s) selected from the group consisting of aryl and heterocyclyl,
(c) cycloalkyl,
(d) aryl which may be substituted with one or more substituent(s) selected from the group consisting of
lower alkyl,
aryl which may be further substituted with hydroxy(s),
lower alkoxy,
aryloxy,
hydroxy, and
halogen,
(e) heterocyclyl which may be substituted with one or more substituent(s) selected from the group consisting of
lower alkyl,
aryl which may be further substituted with halogen(s), and
halogen,
(f) aryloxy, or
(g) amino which may be substituted with aryl(s) which may be further substituted with one or more substituent(s) selected from the group consisting of aryl and heterocyclyl];
or
(2) lower alkyl which may be substituted with

aryl(s) or heterocyclyl(s), each of which may be further substituted with aryl(s); and

R^5 and R^6 are independently hydrogen or lower alkyl; or

R^6 and Y may be linked together to form $-(CH_2)_m-$ (wherein m is 2, 3, 4 or 5);

or a pharmaceutically acceptable salt thereof.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Therefore, the "lower alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like. It is preferably (C1-C4)alkyl, more preferably (C1-C2)alkyl, most preferably methyl.

The "lower alkenyl" means a straight or branched chain aliphatic hydrocarbon having more than one double bond between two carbon atoms, such as ethenyl, 1-methylethenyl, 1-propenyl, 2-propenyl, 1-methyl-1-propenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, pentenyl, hexenyl, and the like, and it is preferably (C2-C5)alkenyl, more preferably (C2-C3)alkenyl, most preferably ethenyl.

The "cycloalkyl" means C3-C10 cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, and

the like, and it is preferably (C5-C6)cycloalkyl.

The "aryl" means an aromatic hydrocarbon group, such as phenyl, naphthyl, indenyl, and the like, and it is preferably (C6-C10)aryl, more preferably naphthyl or phenyl, most preferably phenyl.

The "heterocyclyl" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero atom selected from nitrogen, sulfur and oxygen atom. The group preferably includes, for example:

saturated monocyclic heterocyclic group having 3 to 8-membere containing 1 to 4 nitrogen atom(s), such as pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azacycloheptyl, azacyclooctyl, perhydroazepinyl, and the like;

monocyclic heteroaryl group containing 1 to 4 nitrogen atom(s), such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, pyrimidinyl, pyrazinyl, dihydropyridazinyl, tetrahydropyridazinyl, triazolyl (e.g., 1H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, and the like), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, and the like), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, and the like);

condensated heteroaryl group containing 1 to 5 nitrogen atom(s), such as indolyl, 2,3-dihydroindolyl, isoindolyl, indolyl, 1-methylindolyl, indazolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolinyl, 1,2,3,4-tetrahydroquinolyl, isoquinolyl, benzotriazolyl, tetrazolopyridyl, imidazopyridinyl, methylimidazopyridinyl, tetrazolo-pyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, and the like), dihydrotriazolopyridazinyl, quinoxalinyl;

monocyclic heteroaryl group having 3 to 8-membere

containing 1 to 4 oxygen atom(s), such as furyl, pyranyl, and the like;

condensated heteroaryl group containing 1 to 4 oxygen atom(s), such as benzofuranyl, chromenyl, and the like;

monocyclic heteroaryl group having 3 to 8-membere containing 1 to 2 sulfur atom(s), such as thienyl, thiepinyl, and the like;

condensated heteroaryl group containing 1 to 5 sulfur atom(s), such as benzothienyl, naphto[2,3-b]thienyl, thianthrenyl, benzothienyl, benzothieteyl;

saturated monocyclic heterocyclic group having 3 to 8-membere containing 1 to 3 nitrogen atom(s) and 1 to 2 oxygen atom(s), such as morpholino, and the like;

monocyclic heteroaryl group having 3 to 8-membere containing 1 to 3 nitrogen atom(s) and 1 to 2 oxygen atom(s), such as oxazolyl, isoxazolyl, dihydroisoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 2,5-oxadiazolyl, and the like);

condensated heteroaryl group containing 1 to 3 nitrogen atom(s) and 1 to 2 oxygen atom(s), such as benzoxazolyl, benzoxadiazolyl, and the like;

saturated monocyclic heterocyclic group having 3 to 8-membere containing 1 to 3 nitrogen atom(s) and 1 to 2 sulfur atom(s), such as thiazolidinyl;

monocyclic heteroaryl group having 3 to 8-membere containing 1 to 3 nitrogen atom(s) and 1 to 2 sulfur atom(s), such as thiazolyl, isothiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl);

condensated monocyclic heteroaryl group containing 1 to 3 nitrogen atom(s) and 1 to 2 sulfur

atom(s), such as benzothiazolyl, benzothiadiazolyl, and the like.

The "(lower)alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, and the like. It is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy.

The "(lower alkyl)amino" means a amino group substituted by the above lower alkyl group, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, pentylamino, hexylamino, and the like. It is preferably [(C1-C4)alkyl]amino, more preferably [(C1-C2)alkyl]amino.

The "(lower alkyl)thio" means a sulfur atom (II) substituted by the above lower alkyl group, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio, pentylthio, hexylthio, and the like. It is preferably [(C1-C4)alkyl]thio, more preferably [(C1-C2)alkyl]thio.

The "aryloxy" means oxy group substituted with the above aryl, and includes phenyloxy, naphthyloxy, indenyloxy, and the like, and it is preferably phenyloxy.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, more preferably a fluorine atom or a chlorine atom, most preferably a chlorine atom.

The "amidated carboxy" may include carbamoyl which may be substituted with aryl-(lower alkyl), e.g., benzyl, phenylethyl, phenylpropyl, or the like.

The "(lower alkoxy)carbonyl" means a carbonyl group substituted with lower alkoxy group mentioned

above, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, and the like, and it is preferably [(C1-C4)alkoxy]carbonyl.

The "(lower alkanoyl)oxy" means a formyloxy and a (lower alkyl)carbonyloxy group such as acetyloxy, propionyloxy, butyryloxy, tert-butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy, hexanoyloxy, and the like. It is preferably [(C1-C4)alkanoyl]oxy (including formyloxy).

The "aryl-(lower alkyl)", "(lower alkoxy)-(lower alkyl)", "(lower alkyl)amino-(lower alkyl)", "(lower alkyl)thio-(lower alkyl)" and "carboxy-(lower alkyl)" mean the above lower alkyl group substituted with the above aryl, lower alkoxy, (lower alkyl)amino, (lower alkyl)thio and carboxy, respectively.

The "aryl-(lower alkoxy)" and "heterocyclyl-(lower alkoxy)" mean the above lower alkyl group substituted with the above aryl and heterocyclyl, respectively. For example, "aryl-(lower alkoxy)" may include benzyloxy, 1-phenylethoxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, naphthylmethoxy, 2-naphthylethoxy, and the like. It is preferably phenyl-(lower alkoxy), more preferably phenyl[(C1-C4)alkoxy], more preferably phenyl[(C1-C2)alkoxy], most preferably benzyloxy.

In case where the above groups are substituted, the number of substituent may be two or more if feasible. When the number of substituent is plural, they may be identical or different to each other. In addition, the substituted position is not also limited. For example, when "aryl-(lower alkyl)" is substituted, the substituted position may be aryl moiety or lower alkyl moiety.

The Compound (I) contains one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. The present invention includes both mixtures and separate individual isomers. However, at the carbon bonded by X, Y and N in Compound (I), (S) isomer is more preferable.

The compounds of the formula (I) may also exist in tautomeric forms and this invention includes both mixtures and separate individual tautomers.

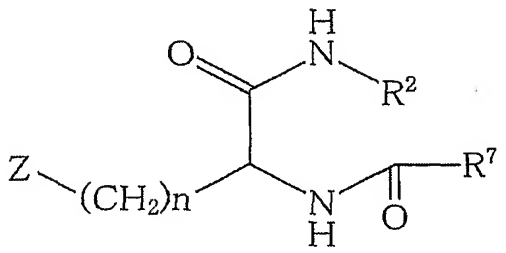
The Compound (I) and their salt may be in a form of a solvate such as hydrate. Such a solvate is included within the scope of the present invention.

Also radiolabelled derivatives of Compound (I) which is suitable for biological studies are included in the scope of the present invention.

In the scope of the present invention, the prodrug of the Compound (I) is included, such a prodrug is capable of undergoing metabolic conversion to Compound (I) following administration in body. Further, in the scope of the present invention, metabolites of Compound (I) is included, which metabolites are therapeutically active in the treatment of the targeted medical condition.

The compound of the present invention can be converted to salt according to a conventional method. Suitable salt of the compounds (I) is pharmaceutically acceptable conventional non-toxic salts and include an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, or the like), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, or the like), a salt with an amino acid (e.g., aspartate, glutamate, or the like), or the like.

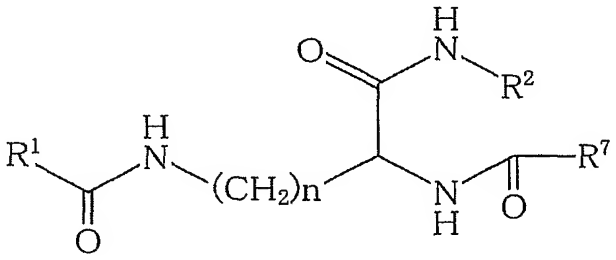
Preferred embodiments of the Compound (I) is Compound (Ia) as follows:



(Ia)

wherein R^2, R^7, n and Z are as defined above.

More preferred embodiments of the Compound (I) is Compound (Ib) as follows:



(Ib)

wherein R^1, R^2, R^7 and n are as defined above.

As Compound (Ib), the compound having the following definition is more preferable:

R^1 is aryl-(lower alkoxy);

R^2 is lower alky, or

aryl which may be substituted with carboxy-(lower alkyl);

R^7 is heterocyclyl which may be substituted with substituted with lower alkyl; and

n is 1, 2, 3, 4 or 5.

In the each definition of the Compound (I), preferably,

(1) X is -CO-;

(2) X is or $-(CH_2)_k-$ (wherein k is 1, 2 or 3);

(3) Y is lower alkyl;

(4) Y is $Z-(CH_2)_n-$, wherein Z is aryl, n is 1, 2, 3, 4, 5 or 6;

(5) Y is $Z-(CH_2)_n-$, wherein Z is $R^1-CO-NR^4-$; wherein R^1 is aryl or heterocyclyl, each of which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, halogen and hydroxy; R^4 is hydrogen; and n is 1, 2, 3, 4, 5 or 6;

(6) Y is $Z-(CH_2)_n-$, wherein Z is $R^1-CO-NR^4-$; wherein R^1 is aryl-(lower alkyl) which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, halogen and hydroxy; R^4 is hydrogen; and n is 1, 2, 3, 4, 5 or 6;

(7) Y is $Z-(CH_2)_n-$, wherein Z is $R^1-CO-NR^4-$; wherein R^1 is aryl-(lower alkoxy) or heterocyclyl-(lower alkoxy), each of which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, halogen and hydroxy; R^4 is hydrogen; and n is 1, 2, 3, 4, 5 or 6;

(8) Y is $Z-(CH_2)_n-$, wherein Z is $R^1-CO-NR^4-$; wherein R^1 is aryl-(lower alkoxy) which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, halogen and hydroxy; R^4 is hydrogen; and n is 1, 2, 3, 4, 5 or 6;

(9) Y is $Z-(CH_2)_n-$, wherein Z is $R^1-CO-NR^4-$; wherein R^1 is phenyl-(lower alkoxy) which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, halogen and hydroxy; R^4 is hydrogen; and n is 4, 5 or 6;

(10) Y is $Z-(CH_2)_n-$, wherein Z is $R^1-CO-NR^4-$; wherein

R^1 is benzyl which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, halogen and hydroxy; R^4 is hydrogen; and n is 4, 5 or 6;

(11) R^2 is aryl-(lower alkyl) which may be substituted with one or more substituent(s) selected from the group consisting of heterocyclyl, carboxy, carboxy-(lower alkyl), amidated carboxy, (lower alkoxy)carbonyl which may be substituted with cycloalkyl, heterocyclyl or (lower alkanoyl)oxy; and cyano;

(12) R^2 is aryl which may be substituted with lower alkyl, lower alkenyl, aryl, lower alkoxy, (lower alkyl)amino, (lower alkyl)thio, carboxy, (lower alkoxy)carbonyl, (lower alkoxy)-(lower alkyl), (lower alkyl)amino-(lower alkyl) or (lower alkyl)thio-(lower alkyl), each of which may be further substituted with one or more substituent(s) selected from the group consisting of heterocyclyl, (lower alkoxy)carbonyl, carboxy and amidated carboxy;

(13) R^2 is aryl which may be substituted with lower alkyl, lower alkenyl, lower alkoxy, (lower alkyl)amino, (lower alkyl)thio, carboxy, (lower alkoxy)carbonyl, (lower alkoxy)-(lower alkyl), (lower alkyl)amino-(lower alkyl) or (lower alkyl)thio-(lower alkyl), each of which may be further substituted with one or more substituent(s) selected from the group consisting of (lower alkoxy)carbonyl, carboxy and carbamoyl;

(14) R^2 is phenyl which may be substituted with (C1-C4)alkyl, (C2-C4)alkenyl, (C1-C4)alkoxy or (C1-C4)amino, each of which may be further substituted with one or more substituent(s) selected from the group consisting of (lower

alkoxy)carbonyl, carboxy and carbamoyl;

(15) R^2 is phenyl which may be substituted with (C1-C4)alkyl, (C2-C4)alkenyl or (C1-C4)alkoxy, each of which may be further substituted with carboxy;

(16) R^3 is $-Q-R^7$, wherein Q is -CO-, R^7 is (a) lower alkyl which may be substituted with one or more substituent(s) selected from the group consisting of cycloalkyl, aryl which may be further substituted with aryl(s), and heterocyclyl, (b) lower alkenyl which may be substituted with one or more substituent(s) selected from the group consisting of aryl and heterocyclyl, (c) cycloalkyl, (d) aryl which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, aryl which may be further substituted with hydroxy(s), lower alkoxy, aryloxy, hydroxy, and halogen, (e) heterocyclyl which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, aryl which may be further substituted with halogen(s), and halogen, (f) aryloxy, or (g) amino which may be substituted with aryl(s) which may be substituted with one or more substituent(s) selected from the group consisting of aryl and heterocyclyl;

(17) R^3 is $-Q-R^7$, wherein Q is -CO-, R^7 is (d) aryl which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, aryl which may be further substituted with hydroxy(s), lower alkoxy, aryloxy, hydroxy, and halogen, (e) heteroaryl which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, aryl which may be further substituted with

halogen(s), and halogen;

(18) R^3 is $-Q-R^7$, wherein Q is -CO-, R^7 is heteroaryl which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl, aryl which may be further substituted with halogen(s), and halogen;

(19) R^3 is $-Q-R^7$, wherein Q is -CO-, R^7 is nitrogen atom containing condensated heteroaryl or nitrogen atom containing monocyclic heteroaryl which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl and halogen;

(20) R^3 is $-Q-R^7$, wherein Q is -CO-, R^7 is nitrogen atom containing condensated heteroaryl which may be substituted with one or more substituent(s) selected from the group consisting of (C1-C4)alkyl;

(21) R^3 is $-Q-R^7$, wherein Q is -CO-, R^7 is oxygen atom containing condensated heteroaryl or oxygen atom containing monocyclic heteroaryl which may be substituted with one or more substituent(s) selected from the group consisting of lower alkyl and halogen;

(22) R^3 is $-Q-R^7$, wherein Q is -CO-, R^7 is oxygen atom containing condensated heteroaryl which may be substituted with one or more substituent(s) selected from the group consisting of (C1-C4)alkyl;

(23) R^5 is hydrogen or (C1-C4)alkyl;

(24) R^5 is hydrogen;

(25) R^6 is hydrogen or (C1-C4)alkyl;

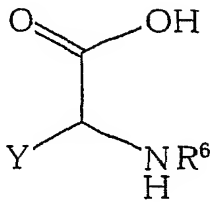
(26) R^6 is hydrogen.

The Compound (I) is preferably selected from: sodium 6-{(2S)-2-[(1-benzofuran-2-yl-carbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino}-hexanoate,

(2E)-3-{2-[(2S)-2-[(1H-indol-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}-acrylic acid,
(2E)-3-{2-[(2S)-2-[(1-methyl-1H-indol-2-yl-carbonyl)amino]-5-[benzyloxycarbonylamino]-pentanoylamino]phenyl}acrylic acid,
3-{2-[(2S)-2-[(1-methyl-1H-indol-2-ylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino]-phenyl}propanoic acid,
sodium 3-{2-[(2S)-2-[(2-quinolinylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}-propanoate,
6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-2-naphthoic acid,
3-{2-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(8-methylimidazo[1,2-a]pyridin-2-yl)carbonyl]amino}-pentanoyl)amino]phenyl}propanoic acid,
3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-quinolinylmethyl)amino]pentanoyl}amino)-phenyl]propanoic acid, and
3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(1H-indol-2-ylcarbonyl)amino]pentanoyl}amino)phenyl]-propanoic acid.

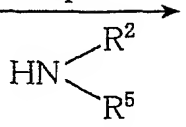
The processes for preparing Compound (I) of the present invention, especially the typical compounds (Ia) and (Ib), are explained in the following processes 1-1 to 2.

Process1-1

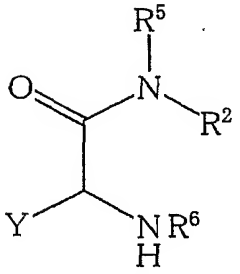


(IIa)
or its reactive derivative at carboxy grunp, or the salt thereof

step a

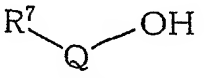


(IIIa)
or its reactive derivative at amino grunp, or the salt thereof

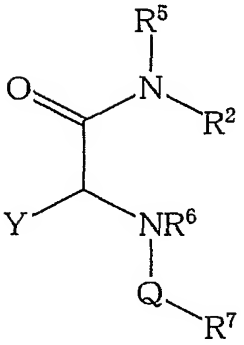


(IVa)
or its salt

step b

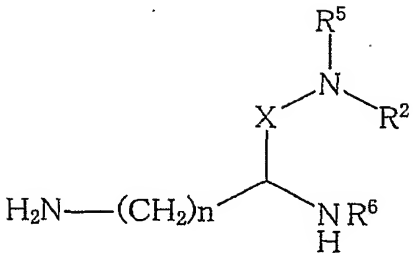


(V)
or its reactive derivative at carboxy grunp, or the salt thereof



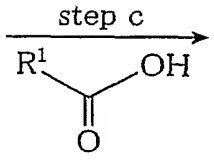
(Ia-1)
or its salt

Process1-2

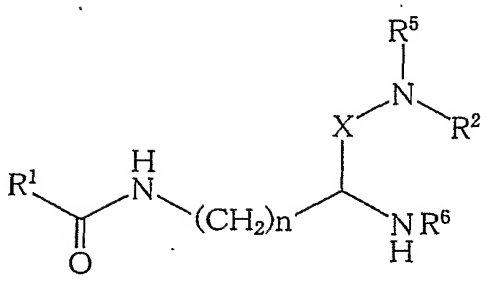


(IIb)
or its reactive
derivative at
amino grunp,
or the salt thereof

step c

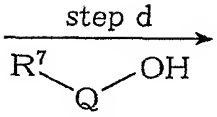


(IIIb)
or its reactive
derivative at
carboxy grunp,
or the salt thereof

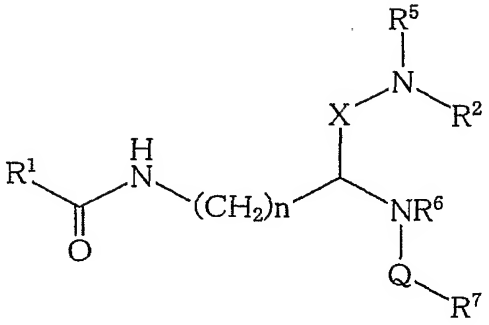


(IVb)
or its salt

step d

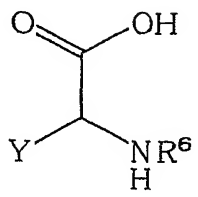


(V)
or its reactive
derivative at
carboxy grunp,
or the salt thereof

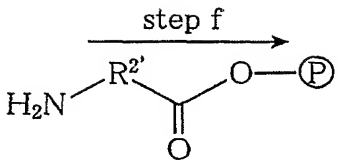


(Ib-1)
or its salt

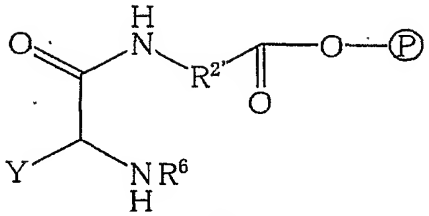
Process2



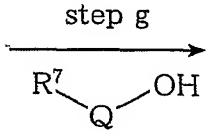
(II a)
or its reactive
derivative at
carboxy grunp,
or the salt thereof



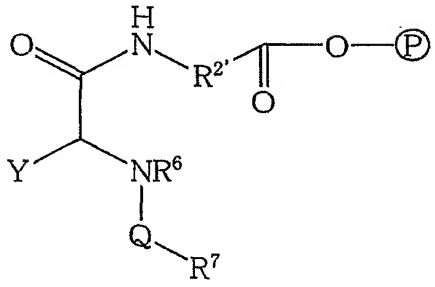
(III c)
or its reactive
derivative at
amino grunp,
or the salt thereof



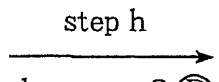
(IV c)
or its salt

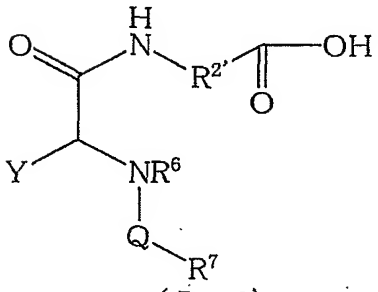


(V)
or its reactive
derivative at
carboxy grunp,
or the salt thereof



(I a-2')
or its salt





(I a-2)
or its salt

[wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, Q, X, Y, Z and n are each as defined above; and

$R^{2'}$ is (1) lower alkyl, (lower alkyl)thio-(lower alkyl) or aryl-(lower alkyl); or

(2) aryl which may be substituted with lower alkyl, lower alkenyl, aryl, lower alkoxy, (lower alkyl)amino,

(lower alkyl)thio,
(lower alkoxy)-(lower alkyl),
(lower alkyl)amino-(lower alkyl), or
(lower alkyl)thio]-(lower alkyl).]

Process 1-1

The compound (Ia-1) or its salt can be prepared by the following steps:

[step a] reacting the compound (IIa) or its reactive derivative at the carboxy group, or the salt thereof, with the compound (IIIa) or its reactive derivative at the amino group, or the salt thereof to give the compound (IVa) or its salt; and

[step b] reacting the obtained compound (IVa) or its salt, with the compound (V) or its reactive derivative at the carboxy group (in case of Q is -CO-)/the sulfo group (in case of Q is $-SO_2-$), or the salt thereof.

[step a] in Process 1-1

In this process, the amine compound (IIIa) can be used on sale or can be synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds.

Suitable reactive derivative of the amine compound (IIIa) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (IIIa) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (IIIa) with a silylating reagent such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide, or the like.

Suitable reactive derivative of the carboxylic acid compound (IIa) may include an acyl halide

(carbonyl chloride, carbonyl bromide, and the like.), an acid anhydride, an acid activated amide, an activated ester, or the like.

Suitable acid anhydride may be a symmetric anhydride or a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid), dialkylphosphorous acid, sulfuric acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid), alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid); aromatic carboxylic acid (e.g., benzoic acid, chlorobenzoic acid, fluorobenzoic acid, nitrobenzoic acid), or the like.

Suitable activated amide may be imidazolylamide, 4-substituted imidazolylamide, dimethylpyrazolyl-amide, triazolylamide, tetrazolylamide, or the like.

Suitable activated ester may be dimethyliminomethyl [$(CH_3)_2N^+=CH-$] ester, vinyl ester, propargyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, methanesulfonylphenyl ester, phenyl thioester, p-nitrophenyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, 8-quinolyl thioester, an activated ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2H-pyridone, N-hydroxysuccinimide, N-hydroxybenzotrioxazole, N-hydroxyphthalimide,), or the like.

When the carboxylic acid compound (IIa) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of condensing agent.

Suitable condensing agent may include a carbodiimide [e.g., N,N'-diisopropylcarbodiimide (DIPCI), N,N'-dicyclohexylcarbodiimide (DCC), N-cyclohexyl-N'-(4-diethylaminocyclohexyl)-carbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide or its hydrochloride], diphenylphosphinic azido, diphenylphosphinic chloride, diethylphosphoryl cyanide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, N,N'-carbonyldiimidoxazole, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, cyanuric chloride, or the like.

The reaction may be also carried out in the presence of organic or inorganic base such as alkali metal carbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, or the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, alcohol [e.g., methanol, ethanol, isopropyl alcohol, or the like], THF, dioxane, toluene, methylene chloride, chloroform, DMF or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not limited and the reaction is usually carried out under cooling to warming.

For example, this reaction can be referred to that of Example 27-1 described later.

[step b] in Process 1-1

(i) in case where Q is -CO-

Suitable reactive derivative of the carboxy compound (V), the condensing agent, base, solvent employable in this process and the reaction temperature

are the same as explained above.

This reaction can be referred to that of Example 27-3.

(ii) in case where Q is $-SO_2-$

Suitable reagent to be used in the sulfonylation is, for example, sulfonyl chloride, sulfonic anhydride (e.g., trifluoromethanesulfonic anhydride) or the like. This reaction is preferably carried out in the presence of base.

Suitable base may include the inorganic base such as alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide), alkaline earth metal hydroxide (e.g., magnesium hydroxide, calcium hydroxide), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate), alkaline earth metal carbonate (e.g., magnesium carbonate calcium carbonate) or the like; and the organic base such as tri(lower)alkylamine {e.g., trimethylamine, diisopropylethylamine (DIPEA) }, pyridine, or the like.

This reaction is usually carried out in a conventional solvent such as toluene, acetonitrile, benzene, DMF, THF, methylene chloride, ethylene chloride, chloroform, or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not limited and the reaction is usually carried out under cooling to warming.

Process 1-2

The compound (Ib-1) or its salt can be prepared by the following steps:

(i) reacting the compound (IIb) or its reactive derivative at the amino group, or the salt thereof, with the compound (IIIb) or its reactive derivative

at the carboxy group, or the salt thereof to give the compound (IVb) or its salt [step c]; and
(ii) reacting the compound (IVb) or its salt, with the compound (V) or its reactive derivative at the carboxy group (in case of Q is -CO-)/the sulfo group (in case of Q is $-SO_2-$), or the salt thereof [step d].

[step c] in Process 1-2

In this process, the compound (IIb) can be obtained in a similar manner to that of [step b] in Process 1-1.

This reaction can be referred to that of Example 36-2 described later.

[step d] in Process 1-2

In this process, the compound (Ib-1) can be obtained in a similar manner to that of [step b] in Process 1-1.

This reaction can be referred to that of Example 27-3 described later.

Process 2

In addition, the compound (I) may be obtained on a solid phase support linkage illustrated above.

For example, the compound (Ia-2) or its salt can be prepared by the following steps:
(i) preparing the resin-bound amine compound (IIIc) [step e];
(ii) reacting the carboxylic acid compound (IIa) or its reactive derivative at the carboxy group, or the salt thereof, with the above resin-bound amine compound (IIIc) or its reactive derivative at the amino group, or the salt thereof to give the amine compound (IVc) or its salt [step f];
(iii) reacting the amine compound (IVc) or its salt,

with the compound (V) or its reactive derivative at the carboxy group (in case of Q is -CO-)/the sulfo group (in case of Q is $-SO_2-$), or the salt thereof [step g]; and

(iv) a cleavage reaction of the resin [step h].

[step e] in Process 2

The resin-bound amine compound (IIIc) is coupled to a solid support such as trytyl-resin by treatment with an activating agent, conveniently 4-nitrophenyl chloroformate in the presence of base such as DIPEA in a solvent such as THF, DMF, dichloromethane, or their mixture.

This reaction can be referred to that of Example 1 described later.

[step f] and [step g] in Process 2

In these processes, the compounds (IVc) and (Ia-2') can be obtained in a similar manner to that of [step b] in Process 1-1.

This reaction can be referred to that of Examples 1 and 27-3.

[step h] in Process 2

Cleavage from the resin is effected, in the case of trytyl resin, by treatment with acid such as trifluoroacetic acid (TFA) as mixture with dichloromethane, or the like.

This reaction can be referred to that of Example 1.

Above processes, all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method.

In the above compounds, which have reactive group, may be protected at the group on cue and be deprotected on cue. In these reactions (protecting or deprotecting steps), concerning the kind of protective group and the condition of the reaction, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC. (the contents of which are hereby incorporated by reference) may be referred.

The patents, patent applications and publications cited herein are incorporated by reference.

For therapeutic purpose, Compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing at least one of said compound as an active ingredient, in admixture with a pharmaceutically acceptable carrier.

The pharmaceutically acceptable carrier can be exemplified by excipient (e.g., sucrose, starch, mannit, sorbit, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate), binding agent (e.g., cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch), disintegrator (e.g., starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxypropylstarch, sodium glycol-starch, sodium bicarbonate, calcium phosphate, calcium citrate), lubricant (e.g., magnesium stearate, talc, sodium laurylsulfate), flavoring agent (e.g., citric acid, mentol, glycine, orange powders), preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben, propylparaben), stabilizer (e.g., citric acid, sodium

citrate, acetic acid), suspending agent (e.g., methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous diluting agent (e.g., water), base wax (e.g., cacao butter, polyethylene-glycol, white petrolatum).

Such a pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form (e.g., tablet, pellet, troche, capsule, suppository, cream, ointment, aerosol, powder, solution, emulsion, suspension, or the like), which contains Compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation.

The pharmaceutical preparations of the present invention may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the Compound (I) depend upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the Compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/kg and about 50 mg/kg, 1 to 4 times per day may be administered.

This application is based on Australian Patent Application No.2003907110 filed on December 22, 2003, the contents of which are hereby incorporated by references.

Although the present invention has been fully described by way of example, it is to be understood that various changes and modifications will be apparent to those skilled in the art. Therefore, unless otherwise such changes and modifications depart from the scope of the present invention hereinafter defined, they should be construed as being included therein.

THE BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Although the present invention has been fully described by way of example, it is to be understood that various changes and modifications will be apparent to those skilled in the art. Therefore, unless such changes and modifications depart from the objective of the present invention, they should be construed as being included therein.

Abbreviations used in this application are as follows:

EtOAc:	ethyl acetate
DMF:	N,N-dimethylformamide
Boc:	tert-butoxycarbonyl
Fmoc:	9-fluorenylmethoxycarbonyl
WSCD:	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride
DIPCI:	1,3-diisopropylcarbodiimide
TBTU:	O-benzotriazole-N,N,N,N'-tetramethyl-uronium-hexafluorophosphate

HOBT: 1-hydroxybenzotriazole
THF: tetrahydrofuran
DIPEA: N,N-diisopropylethylamine
EtOH: ethanol
MeOH: methanol
NMP: 1-methyl-2-pyrrolidinone
BSA: N,O-bis(trimethylsilyl)acetamide
PyBOP: benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
DIEA: N,N-diisopropylethylamine
DMSO: dimethyl sulfoxide
DEAD: diethyl azodicarboxylate
DCM: dichloromethane
Et_2O: diethyl ether
PyBroP: bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
TFA: trifluoroacetic acid
MSNT: 1-(mesitylene-3-sulfonyl)-3-nitro-1H-1,2,4-triazole
Et_2O: diethyl ether
Ac_2O: acetic anhydride
HATU: O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
TISH: triisopropylsilane
Fmoc: 9-fluorenylmethoxycarbonyl
Mtt: (4-methyl)trityl
HPLC: high performance liquid chromatography

Example 1

6-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

A solution of 6-[9-(flouorenylmethoxycarbonyl)-amino]hexanoic acid (180mg) and DIPEA (0.12mL) in

dichloromethane (3mL) was added to a reaction vessel containing Cl-trytyl resin (200mg, 1.3mmol/g, loading). After the vessel was shaken for 12 hours at room temperature, the resin was washed successively with dichloromethane, THF, DMF and dichloromethane.

After cleavage of Fmoc by using 20% piperazine in DMF (5mL), 2-Fmoc-5-[benzyloxycarbonylamino]-pentanoic acid (254mg), TBTU (170mg), HOBT (70mg) and DIPEA (0.18mL) were added to a solution of the obtained resin in DMF (3mL). After the vessel was shaken for 12 hours at room temperature, the resin was washed successively with dichloromethane, THF, DMF and dichloromethane.

After cleavage 9-(flouorenylmethoxy carbonyl)amide by using 20% piperazine in DMF (5mL), benzofuran-2-carboxylic acid (210mg), DIPCI (0.21mL) and DIPEA (0.23mL) were added successively to a solution of the obtained resin in dichloromethane (3mL). After the vessel was shaken for 12 hours at room temperature, the resin was washed successively with dichloromethane, THF, DMF, and dichloromethane.

Cleavage from the resin was performed with 1% trifluoromethanesulfonic acid in dichloromethane (5mL) for 10 minutes at room temperature. After the filtrated solvent was evaporated under pressure, the residue was washed with ether to give the target compound (100mg, 72%).

MS : 524 (M+1).

Example 2

{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}acetic acid

The target compound was obtained in a similar

manner to that of Example 1.

MS : 468 (M+1).

Example 3

4-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}butanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 496 (M+1).

Example 4

5-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}pentanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 510 (M+1).

Example 5

7-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}heptanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 538 (M+1).

Example 6

6-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-3-[benzyloxycarbonylamino]propanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 496 (M+1).

Example 7
6-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-4-[benzyloxycarbonylamino]butanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 510 (M+1).

Example 8
6-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-6-[benzyloxycarbonylamino]hexanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 538 (M+1).

Example 9
6-{(2R)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-6-[benzyloxycarbonylamino]hexanoylamino}hexanoic acid

The target compound was obtained in a similar

manner to that of Example 1.

MS : 538 (M+1).

Example 10
6-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-3-phenylpropanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 423 (M+1).

Example 11
6-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-3-methylbutanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 375 (M+1).

Example 12
6-[(2S)-1-(1-Benzofuran-2-ylcarbonyl)-2-(pyrrolidinyl)carbonylamino]hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 373 (M+1).

Example 13
6-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[ethoxycarbonylamino]pentanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 476 (M+1).

Example 14
6-{(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[benzoylamino]pentanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 494 (M+1).

Example 15
6-{(2S)-2,5-Bis[(1-benzofuran-2-ylcarbonyl)amino]-pentanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 534 (M+1).

Example 16
6-{(2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 540 (M+1).

Example 17
6-{(2S)-2-[(2E)-(3-Phenyl-2-propenoyl)amino]-5-

[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 510 (M+1).

Example 18

6-{(2S)-2-[(4-Biphenylylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 560 (M+1).

Example 19

6-{(2S)-2-[(2-Naphthoyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 534 (M+1).

Example 20

6-{(2S)-2-[(1H-Indol-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 523 (M+1).

Example 21
6-{(2S)-2-[(1H-Indol-3-ylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino}-hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 523 (M+1).

Example 22
6-{(2S)-2-[(1H-Indol-6-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

The target compound was obtained in a similar manner to that of Example 1.

MS : 523 (M+1).

Example 23
Sodium 6-{(2S)-2-[(1-benzofuran-2-yl-carbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino}-hexanoate

To a solution of 6-{(2S)-2-[(1-benzofuran-2-yl-carbonyl)amino]-5-[benzyloxycarbonylamino]-pentanoylamino}hexanoic acid (50mg) obtained in Example 1 in MeOH, was added 1N NaOH (0.1mL) at room temperature. After the solvent was evaporated under pressure, the residue was washed with ether to give the target compound (50mg).

MS : 524 (M+1).

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.2-1.8(10H, m), 1.95(2H, t, J=7.0Hz), 3.03(4H, t, J=6.2Hz), 4.43(1H, m), 4.99(2H s), 7.2-7.6(8H, m), 7.6-7.9(3H, m), 8.31(1H, t, J=5.4Hz), 8.87(1H d, J=8.2Hz).

Example 24

Benzyl N-{(4S)-4-[(1-benzofuran-2-yl-carbonyl)-amino]-5-oxo-5-[(6-oxo-6-benzylaminohexyl)amino]-pentyl}carbamate

To a solution of 6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]-pentanoylamino}hexanoic acid (50mg) obtained in Example 1 in DMF (1mL), were added successively TBTU (84mg), HOBT (18mg), DIPEA (0.023mL) and benzylamine (0.014mL) at room temperature. After stirring for 4 hours, the mixture was diluted with EtOAc. The solution was washed successively with water, 1N HCl, 1N NaOH and brine, and dried over $MgSO_4$. After the filtrated solvent was evaporated under pressure, the residue was washed with ether to give the target compound (40mg).

MS : 613 (M+1).

Example 25

Benzyl N-{(4S)-4-[(1-benzofuran-2-ylcarbonyl)-amino]-5-oxo-5-[6-oxo-6-[(2-phenylethylamino-hexyl)amino]pentyl]carbamate

The target compound was obtained in a similar manner to that of Example 24.

MS : 627 (M+1).

Example 26

Benzyl N-{(4S)-4-[(1-benzofuran-2-ylcarbonyl)-amino]-5-oxo-5-[6-oxo-6-[(3-phenylpropylamino-hexyl)amino]pentyl]carbamate

The target compound was obtained in a similar manner to that of Example 24.

MS : 641 (M+1).

Example 27-1

Methyl (2E)-3-{2-[(2S)-5-[benzyloxycarbonylamino]-2-[tert-butoxycarbonylamino]pentanoylamino]-phenyl}acrylate

To a solution of (2S)-2-(tert-butoxycarbonylamino)-5-(benzyloxycarbonylamino)-pentanoic acid (6.00g) and methyl (2E)-3-(2-aminophenyl)acrylate (3.77g) in DMF (60mL), were added successively HOBT (3.32g), WSCD (6.28g) and 4-(dimethylamino)pyridine (400mg). The mixture was stirred at 50℃ for 15 hours.

After cooling to room temperature, the mixture was quenched by the addition of water (120mL) and extracted with EtOAc (120mL). The extract was washed successively with water (120mL), saturated aqueous sodium hydrogencarbonate (120mL), 1N HCl (120mL), water (120mL) and brine (120mL), and dried over $MgSO_4$. Filtration followed by evaporation gave a crude product which was chromatographed on silica gel (eluent: hexane/EtOAc=1/1) to give the target compound (2.58g) as a yellow crystalline solid.

MS ((+)ESI) m/z : 548 $(M+Na)^+$.

Example 27-2

Methyl (2E)-3-{2-[(2S)-2-amino-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}acrylate hydrochloride

To a suspension of methyl (2E)-3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}-acrylate (2.58g) obtained in Example 27-1 in EtOAc (20mL), was added 4N hydrogen chloride in EtOAc (20mL). The mixture was stirred at room temperature for 1 hour. The solvent was removed by evaporation to give the target compound (2.40g) as a yellow solid.

MS ((+)ESI) m/z : 426 $(M+H)^+$, 448 $(M+Na)^+$.

Example 27-3

Methyl (2E)-3-{2-[(2S)-2-[(1H-indol-2-ylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino]-phenyl}acrylate

To a solution of methyl (2E)-3-{2-[(2S)-2-amino-5-[benzyloxycarbonyl-amino]pentanoylamino]phenyl}acrylate hydrochloride (400mg) obtained in Example 27-2 in DMF (4.0mL), were added successively indole-2-carboxylic acid (154mg), HOBT (176mg) and WSCD (0.32mL). The mixture was stirred at room temperature for 16 hours. The mixture was diluted with EtOAc (10mL) and washed with water (10mL×2). The organic layer was stirred vigorously at room temperature for 1 hour. The precipitates were collected by filtration, washed with EtOAc (1mL×2), and dried under reduced pressure to give the target compound (115mg) as a white solid.

MS ((+)ESI) m/z : 591 $(M+Na)^+$.

Example 28

(2E)-3-{2-[(2S)-2-[(1H-Indol-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}-acrylic acid

To a suspension of methyl (2E)-3-{2-[(2S)-2-[(1H-indol-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}-acrylate (109mg) obtained in Example 27-3 in MeOH (2.0mL) and THF (2.0mL), was added 1N NaOH (0.38mL). The mixture was refluxed for 2 hours. After cooling to room temperature, the mixture was quenched by the addition of 1N HCl (20mL) and extracted with EtOAc (20mL). The extract was washed with water (20mL) and brine (20mL), and dried over $MgSO_4$. Filtration followed by evaporation gave the target compound (102mg) as a pale yellow solid.

MS ((-)ESI) m/z : 553 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.61-1.99(4H, m), 3.05-3.11(2H, m), 4.63-4.79(1H, m), 5.01(2H, s), 6.49(1H, d, J=15.9Hz), 7.00-7.83(16H, m), 8.61(1H, d, J=7.7Hz), 10.0(1H, br-s), 11.6(1H, br-s),12.9(1H, br-s).

Example 29

Methyl (2E)-3-{2-[(2S)-2-[(1-methyl-1H-indol-2-yl-carbonyl)amino]-5-[benzyloxycarbonylamino]-pentanoylamino]phenyl}acrylate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 605 $(M+Na)^+$.

Example 30

(2E)-3-{2-[(2S)-2-[(1-Methyl-1H-indol-2-yl-carbonyl)amino]-5-[benzyloxycarbonylamino]-pentanoylamino]phenyl}acrylic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 567 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.61-1.99(4H, m), 3.09-3.11(2H, m), 3.99(3H, s), 4.60-4.71(1H, m), 5.01(2H, s), 6.49(1H, d, J=15.9Hz), 7.07-7.84(16H, m), 8.62(1H, d, J=7.7Hz), 9.97(1H, br-s), 12.4(1H, br-s).

Example 31

Methyl (2E)-3-{2-[(2S)-2-[(4-biphenylylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino]-phenyl}acrylate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 628 $(M+Na)^+$.

Example 32

(2E)-3-{2-[(2S)-2-[(4-Biphenylylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}-acrylic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 590 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.60-1.99(4H, m), 3.08-3.11(2H, m), 4.64-4.79(1H, m), 5.01(2H,s), 6.48(1H, d, J=15.9Hz), 7.19-7.54(12H, m), 7.73-7.83(6H, m), 8.04(2H, d, J=8.4Hz), 8.66(1H, d, J=7.5Hz), 9.97(1H, br-s), 12.4(1H, br-s).

Example 33
Methyl (2E)-3-{2-[(2S)-2-[(1-benzofuran-2-yl-carbonyl)amino]-5-[benzyloxycarbonylamino]-pentanoylamino]phenyl}acrylate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 592 $(M+Na)^+$.

Example 34-1
Methyl 3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-[aminopentanoylamino]phenyl}propanoate

To a solution of methyl (2E)-3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyloxy-carbonylamino]pentanoylamino]phenyl}acrylate (1.30g) obtained in Example 33 in MeOH (26mL) and THF (26mL), was added 10% palladium on activated carbon (50% wet, 130mg). The mixture was hydrogenated (1 atm) at room temperature for 90 minutes. The catalyst was removed by filtration through a Celite cake and washed with MeOH. The filtrate was concentrated in vacuo to give the target compound (1.19g) as a white solid.

Example 34-2
Methyl 3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino]-

phenyl}propanoate

To a solution of methyl 3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-aminopentanoylamino]phenyl}propanoate (1.05g) obtained in Example 34-1 in THF (10mL) and water (10mL), was added benzyl chloroformate (0.38mL) at 5℃ while the pH was adjusted to 8.0~9.0 by the addition of 10% aqueous NaOH.

After stirring at the same temperature for 30 minutes, the mixture was extracted with EtOAc (20mL). The extract was washed with water (20mL) and brine (20mL), and dried over $MgSO_4$. Filtration followed by evaporation gave a crude solid which was purified by silica gel chromatography (eluent: hexane/EtOAc=1/1) and recycling preparative HPLC equipped with a gel permeation chromatography column (eluent: chloroform) to give the target compound (572mg) as a white crystalline solid.

MS ((+)ESI) m/z : 594 $(M+Na)^+$.

Example 35

3-{2-[(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}-propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 556 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.57-1.99(4H, m), 2.45-2.51(2H, m), 2.78-2.85(2H, m), 3.06-3.09(2H, m), 4.65-4.68(1H, m), 5.00(2H, s), 7.11-7.52(12H, m), 7.66-7.81(3H, m), 8.75(1H, d, J=7.7Hz), 9.62(1H, br-s),

12.2(1H, br-s).

Example 36-1

Methyl (2E)-3-{2-[(2S)-2-[tert-butoxycarbonyl-amino]-5-amino-pentanoylamino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 34-1.

MS ((+)ESI) m/z : 394 $(M+H)^+$.

Example 36-2

Methyl 3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-[(2-chlorobenzyloxycarbonyl)amino]pentanoylamino]-phenyl}propanoate

To a solution of methyl (2E)-3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-aminopentanoylamino]phenyl}propanoate (4.34g) obtained in Example 36-1 in dichloromethane (80mL), was added triethylamine (2.31mL). The solution was cooled to 5℃. To the solution was added 2-chlorobenzyl chloroformate (1.86mL) at 5℃, and the mixture was stirred at the same temperature for 1 hour.

The solvent was removed by evaporation, and the residue was partitioned between 1N HCl (80mL) and EtOAc (80mL). The organic layer was separated, washed successively with water (80mL), saturated aqueous sodium hydrogencarbonate (80mL) and brine (80mL), and dried over $MgSO_4$. Filtration followed by evaporation gave a yellow solid which was chromatographed on silica gel (eluent:hexane/EtOAc=2/1 to 3/2) to give the target compound (3.62g) as a white solid.

MS ((+)ESI) m/z : 584 $(M+Na)^+$.

Example 36-3
Methyl 3-{2-[(2S)-2-amino-5-[(2-chlorobenzyloxy-carbonyl)amino]pentanoylamino]phenyl}propanoate hydrochloride

To a suspension of methyl 3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-[(2-chlorobenzyloxy-carbonyl)amino]pentanoylamino]phenyl}propanoate (3.45g) obtained in Example 36-2 in EtOAc (15mL), was added 4N hydrogen chloride in EtOAc (45mL). The mixture was stirred at room temperature for 1 hour. The mixture was concentrated in vacuo to give the target compound (3.11g) as a pale yellow viscous oil.

MS ((+)ESI) m/z : 462 $(M+H)^+$.

Example 36-4
Methyl 3-{2-[(2S)-2-[(1-benzofuran-2-yl-carbonyl)-amino]-5-[(2-chlorobenzyloxycarbonyl)amino]-pentanoylamino}phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

Example 37
3-{2-[(2S)-2-[(1-Benzofuran-2-yl-carbonyl)amino]-5-[(2-chlorobenzyloxycarbonyl)amino]pentanoyl-amino]phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 590 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.59-1.99(4H, m),

2.45-2.50(2H, m), 2.78-2.85(2H, m), 3.07-3.10 (2H, m), 4.66-4.69(1H, m), 5.09(2H, s), 7.11-7.52(11H, m),7.66-7.81(3H, m), 8.74(1H, d, J=7.6Hz), 9.61 (1H, br-s), 12.1(1H, br-s).

Example 38-1

Methyl 3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-[(benzyloxycarbonyl)amino]pentanoylamino]phenyl}-propanoate

The target compound was obtained in a similar manner to that of Example 36-2.

MS ((+)ESI) m/z : 550 $(M+Na)^+$.

Example 38-2

Methyl 3-{2-[(2S)-2-amino-5-[benzyloxycarbonyl-amino]pentanoylamino]phenyl}propanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 36-3.

MS ((+)ESI) m/z : 428 $(M+H)^+$.

Example 38-3

Methyl 3-{2-[(2S)-2-[(1-methyl-1H-indol-2-yl-carbonyl)amino]-5-[benzyloxycarbonylamino]-pentanoylamino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 607 $(M+Na)^+$.

Example 39
3-{2-[(2S)-2-[(1-Methyl-1H-indol-2-ylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino]-phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 569 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.59-1.91(4H, m), 2.48-2.54(2H,m), 2.79-2.87(2H, m), 3.05-3.10(2H, m), 3.98(3H, s), 4.55-4.66(1H, m), 5.01(2H, s), 7.07-7.35(13H, m), 7.53(1H, d, J=8.3Hz), 7.65(1H, d, J=7.9Hz), 8.62(1H, d, J=7.6Hz), 9.56(1H, br-s), 12.1(1H, br-s).

Example 40
Methyl 3-{2-[(2S)-2-[(2-quinolinylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino]-phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 605$(M+Na)^+$.

Example 41
Sodium 3-{2-[(2S)-2-[(2-quinolinylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}-propanoate

To a suspension of methyl 3-{2-[(2S)-2-[(2-quinolinylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]-phenyl}-propanoate (100mg) obtained in Example 40 in EtOH

(2.0mL), was added 1N NaOH (0.343mL). The mixture was refluxed for 10 minutes. The resulting solution was allowed to cool to room temperature, stirred for 16 hours, and concentrated in vacuo. The residual solid was dissolved in EtOH (2.0mL) and the solution was stirred at room temperature for 2 hours. The resulting precipitates were collected by filtration, washed with EtOH, and dried under reduced pressure at 60℃ to give the target compound (79.3mg) as a white solid.

MS ((-)ESI) m/z : 567 $(M-Na)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.55-1.58(2H, m), 1.95-2.06(2H, m), 2.27-2.30(2H, m), 2.73-2.74(2H, m), 3.12-3.14(2H, m), 4.86-4.88(1H, m), 4.98(2H, s), 7.00-7.32(8H, m), 7.70-7.90(4H, m), 8.11(1H, d, J=8.1Hz), 8.21(2H, d, J=8.5Hz), 8.61(1H, d, J=8.5Hz), 9.01(1H, d, J=8.4Hz), 13.1(1H, br-s).

Example 42-1

Methyl 4-[2-({(2S)-5-{[benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-ethyl]benzoate

To a suspension of (2S)-5-[[(benzyloxy)-carbonyl]amino]-2-[(tert-butoxycarbonyl)amino]-pentanoic acid (1.00g) and methyl 4-(2-aminoethyl)benzoate hydrochloride (647mg) in N,N-dimethylformamide (20mL), were added HOBT (3.32g), and WSCD (553 mg) at room temperature. The mixture was stirred for 2 hours.

The mixture was quenched by the addition of water (40mL) and extracted with ethyl acetate (40mL×1). The extract was washed with water (40mL×2), saturated aqueous sodium hydrogencarbonate (40mL×1) and brine (40mL×1), and then dried over magnesium sulfate.

Filtration followed by evaporation gave the target compound (1.45g) as a pale yellow solid.

MS ((+)ESI) m/z : 550 $(M+Na)^+$.

Example 42-2

Methyl 4-{2-[((2S)-2-amino-5-{[(benzyloxy)-carbonyl]amino}pentanoyl)amino]ethyl}benzoate hydrochloride

Methyl 4-[2-[[(2S)-5-[[(benzyloxy)carbonyl]-amino]-2-[(tert-butoxycarbonyl)amino]pentanoyl]-amino]ethyl]benzoate (1.43 g) obtained in Example 42-1 was suspended in 2.5N hydrogen chloride in methanol (14mL). The mixture was stirred at room temperature for 16 hours. The solvent was removed by evaporation to give the target compound (1.27g) as a yellow solid.

MS ((+)ESI) m/z : 450 $(M+Na)^+$.

Example 42-3

Methyl 4-{2-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]ethyl}benzoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 594 $(M+Na)^+$.

Example 43

4-{2-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-ethyl}benzoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 556 $(M-H)^-$.

Example 44-1
Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-2-naphthoate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 572 $(M+Na)^+$.

Example 44-2
Methyl 6-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]-2-naphthoate hydrochloride

The target compound was obtained in a similar manner to that of Example 27-2.

MS ((+)ESI) m/z : 450 $(M+H)^+$.

Example 44-3
Methyl 6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]-2-naphthoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 616 $(M+Na)^+$.

Example 45

6-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-2-naphthoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 578 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.40-2.06(4H, m), 2.96-3.48(4H, m), 4.62-4.73(1H, m), 5.01(2H, s), 7.32-7.98(14H, m), 8.09(1H, d, J=8.5Hz), 8.41(1H, s), 8.54(1H, s), 8.88(1H, d, J=7.5Hz), 10.5(1H, br-s), 13.0(1H, br-s).

Example 46-1
Methyl 3'-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-3-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 598 $(M+Na)^+$.

Example 46-2
Methyl 3'-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]-3-biphenylylcarboxylate hydrochloride

The target compound was obtained in a similar manner to that of Example 27-2.

MS ((+)ESI) m/z : 476 $(M+H)^+$.

Example 46-3

Methyl 3'-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]-3-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 642 $(M+Na)^+$.

Example 47

3'-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-3-biphenylylhenylcarboxylic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 604 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.48-1.66(2H, m), 1.83-1.96(2H, m), 3.07-3.09(2H, m), 4.58-4.69(1H, m), 5.00(2H, s), 7.26-8.01(18H, m), 8.19(1H, s), 8.82(1H, d, J=7.5Hz), 10.3(1H, s), 13.1(1H, br).

Example 48-1

Methyl 3'-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-4-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 598 $(M+Na)^+$.

Example 48-2

Methyl 3'-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-

amino}pentanoyl)amino]-4-biphenylylcarboxylate hydrochloride

The target compound was obtained in a similar manner to that of Example 27-2.

MS ((+)ESI) m/z : 476 $(M+H)^+$.

Example 48-3

Methyl 3'-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]-4-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 642 $(M+Na)^+$.

Example 49

3'-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-4-biphenylylcarboxylic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 604 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.41-1.69(2H, m), 1.80-1.97(2H, m), 3.03-3.09(2H, m), 4.58-4.69(1H, m), 5.01(2H, s), 7.29-7.53(10H, m), 7.65-7.82(6H, m), 8.02-8.06(3H, m), 8.82(1H, d, J=7.5Hz), 10.3(1H, br-s), 13.0(1H, br).

Example 50-1

t-Butyl {2-[((2S)-2-(tert-butoxycarbonyl)amino-

5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-phenoxy}acetate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 594 $(M+Na)^+$.

Example 50-2

Methyl {2-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]phenoxy}acetate hydrochloride

The target compound was obtained in a similar manner to that of Example 42-2.

MS ((+)ESI) m/z : 430 $(M+H)^+$.

Example 50-3

Methyl {2-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]phenoxy}acetate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 596 $(M+Na)^+$.

Example 51

Sodium {2-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]phenoxy}acetate

To a solution of methyl [2-[[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-

[[(benzyloxy)carbonyl]amino]pentanoyl]amino]-phenoxy]acetate (197mg) obtained in Example 50-3 in methanol (2.0mL) and tetrahydrofuran (2.0mL), was added 1N sodium hydroxide solution (0.343mL). The mixture was stirred at room temperature for 20 hours. The solvent was removed by evaporation to give the target compound (220 mg) as a white solid.

MS ((-)ESI) m/z : 558 $(M-Na)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.56-1.97(2H, m), 3.07-3.10(2H, m), 4.20(2H, s), 4.68-4.79(1H, m), 5.00(2H, s), 6.96-7.02(3H, m), 7.33-7.80(11H, m), 8.09-8.13(1H, m), 8.89(1H, d, J=8.5Hz), 12.3(1H, br-s).

Example 52-1

tert-Butyl [3-({(2S)-5-{[(benzyloxy)carbonyl]-amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}-amino)phenoxy]acetate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 594 $(M+Na)^+$.

Example 52-2

Methyl {3-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]phenoxy}acetate hydrochloride

The target compound was obtained in a similar manner to that of Example 42-2.

MS ((+)ESI) m/z : 430 $(M+H)^+$.

Example 52-3
Methyl {3-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]phenoxy}acetate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 594 $(M+Na)^+$.

Example 53
Sodium {3-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]phenoxy}acetate

The target compound was obtained in a similar manner to that of Example 51.

MS ((-)ESI) m/z : 558 $(M-Na)^+$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.40-2.01(4H,m), 3.03-3.06(2H, m), 4.11(2H, s), 4.57-4.60(1H, m), 5.00(2H, s), 6.52(1H, d, J=8.0Hz), 7.06-7.51(11H, m), 7.67-7.80(3H, m), 9.02(1H, d, J=7.5Hz), 10.3(1H, br-s).

Example 54-1
Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}--2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-ethyl]benzoate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 550 $(M+Na)^+$.

Example 54-2

Methyl 3-{2-[((2S)-2-amino-5-{[(benzyloxy)-carbonyl]amino}pentanoyl)amino]ethyl}benzoate hydrochloride

The target compound was obtained in a similar manner to that of Example 27-2.

MS ((+)ESI) m/z : 428 $(M+H)^+$.

Example 54-3

Methyl 3-{2-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]ethyl}benzoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 594 $(M+Na)^+$.

Example 55

3-{2-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-ethyl}benzoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 556 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.30-1.52(2H, m), 1.60-1.82(2H, m), 2.76-2.83(2H, m), 2.95-3.01(2H, m), 3.21-3.43(2H, m), 4.08-4.45(1H, m), 5.00(2H, s), 7.24-7.80(15H, m), 8.15(1H, t, J=5.5Hz), 8.52(1H, d, J=8.0Hz), 12.9(1H, br).

Example 56-1
Methyl 4'-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-3-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 598 $(M+Na)^+$.

Example 56-2
Methyl 4'-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]-3-biphenylylcarboxylate hydrochloride

The target compound was obtained in a similar manner to that of Example 27-2.

MS ((+)ESI) m/z : 498 $(M+Na)^+$.

Example 56-3
Methyl 4'-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]-3-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 642 $(M+Na)^+$.

Example 57
4'-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-3-biphenylylcarboxylic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 604 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.48-1.69(2H, m), 1.82-1.94(2H, m), 3.03-3.13(2H, m), 4.59-4.70(1H, m), 5.01(2H, s), 7.33-7.94(18H, m), 8.18(1H, s), 8.82(1H, d, J=7.5Hz), 10.3(1H, br-s), 13.1(1H, br).

Example 58-1

Methyl 4-[2-({(2S)-5-amino-2-[(1-benzofuran-2-ylcarbonyl)amino]pentanoyl}amino)ethyl]benzoate

The target compound was obtained in a similar manner to that of Example 34-1.

MS ((+)ESI) m/z : 438 $(M+H)^+$.

Example 58-2

Methyl 4-[2-({(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-[(3-phenylpropanoyl)amino]pentanoyl}-amino)ethyl]benzoate

To a solution of methyl 4-[2-[[(2S)-5-amino-2-[(1-benzofuran-2-ylcarbonyl)-amino]pentanoyl]amino]ethyl]benzoate (100mg) obtained in Example 58-1 and 3-phenylpropanoic acid (37.8mg) in N,N-dimethylformamide (2.0mL), were added HOBT (46.3mg) and WSCD (87.6mg). The mixture was stirred at room temperature for 16 hours.

The mixture was diluted with ethyl acetate (10mL), washed successively with water (10mL×2) and brine (10mL), and dried over magnesium sulfate. Filtration followed by evaporation gave a crude product which was chromatographed on silica gel (SiO_2, 25g, eluent:

hexane/ethyl acetate = 33/66 to 0/100) to give the target compound (78.2mg) as a white solid.

MS ((+)ESI) m/z : 592 $(M+Na)^+$.

Example 59

Sodium 4-[2-({(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-[(3-phenylpropanoyl)amino]pentanoyl}-amino)ethyl]benzoate

To a solution of methyl 4-[2-[[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[(3-phenylpropanoyl)amino]pentanoyl]amino]ethyl]-benzoate (71.8mg) obtained in Example 58-2 in methanol (1.0mL) and tetrahydrofuran (1.0mL), was added 1N sodium hydroxide (0.139mL). The mixture was refluxed for 2 hours, at which time the reaction was incomplete. Additional 1N sodium hydroxide (0.025mL) was added and the mixture was refluxed for 4 hours, at which time the starting material was still remained. Additional 1N sodium hydroxide (0.006mL) was added and the mixture was refluxed for 2 hours, at which time the reaction was complete.

After cooling to room temperature, the solvent was removed by evaporation and the residual solid was washed a small amount of methanol, and dried under reduced pressure to give the target compound (23.1mg) as a pale yellow crystalline solid.

MS ((-)ESI) m/z : 554 $(M-Na)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.25-1.36(2H, m), 1.54-1.71(2H, m), 2.32-2.40(2H, m), 2.67-2.83(4H, m), 2.93-3.03(2H, m), 3.18-3.42(2H, m), 4.35-4.45(1H, m), 7.05-7.51(9H, m), 7.64-7.80(5H, m), 8.06(1H, t, J=5.5Hz), 8.18(1H, t, J=5.5Hz), 8.70(1H, d, J=8.0Hz).

Example 60
Methyl 4-{2-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(2R)-2-hydroxy-3-phenylpropanoyl]-amino}pentanoyl)amino]ethyl}benzoate

The target compound was obtained in a similar manner to that of Example 58-2.

MS ((+)ESI) m/z : 608 $(M+Na)^+$.

Example 61
Sodium 4-{2-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(2R)-2-hydroxy-3-phenylpropanoyl]-amino}pentanoyl)amino]ethyl}benzoate

The target compound was obtained in a similar manner to that of Example 59.

MS ((-)ESI) m/z : 570 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.19-1.40(2H, m), 1.54-1.71(2H, m), 2.66-2.82(3H, m), 2.91-3.06(3H, m), 3.17-3.46(2H, m), 4.00-4.06(1H, m), 4.35-4.45(1H, m), 6.38(1H, br), 7.07-7.51(9H, m), 7.65-7.88(6H, m), 8.22(1H, t, J=5.0Hz), 8.59(1H, d, J=8.0Hz).

Example 62
Methyl 4-{2-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(2S)-2-hydroxy-3-phenylpropanoyl]-amino}pentanoyl)amino]ethyl}benzoate

The target compound was obtained in a similar manner to that of Example 58-2.

MS ((+)ESI) m/z : 608 $(M+Na)^+$.

Example 63
Sodium 4-{2-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(2S)-2-hydroxy-3-phenylpropanoyl]-amino}pentanoyl)amino]ethyl}benzoate

The target compound was obtained in a similar manner to that of Example 59.

MS ((-)ESI) m/z : 570 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.23-1.42(2H, m), 1.52-1.74(2H, m), 2.66-2.81(3H, m), 2.92-3.07(2H, m), 3.21-3.43(2H, m), 4.02-4.08(1H, m), 4.35-4.46(1H, m), 6.28(1H, br), 7.08-7.50(9H, m), 7.66-7.90(6H, m), 8.27(1H, t, J=5.0Hz), 8.65(1H, d, J=8.0Hz).

Example 64
Methyl 4-(2-{[(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-({[(2-chlorobenzyl)oxy]carbonyl}amino)-pentanoyl]amino}ethyl)benzoate

The target compound was obtained in a similar manner to that of Example 36-2.

MS ((+)ESI) m/z : 628 $(M+Na)^+$.

Example 65
4-(2-{[(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-({[(2-chlorobenzyl)oxy]carbonyl}amino)-pentanoyl]amino}ethyl)benzoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 590 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.32-1.53(2H, m), 1.60-1.81(2H, m), 2.71-2.87(2H, m), 2.93-3.07(2H, m), 3.21-3.44(2H, m), 4.34-4.45(1H, m), 5.08(2H, s), 7.30-7.86(14H, m), 8.14(1H, t, J=5.0Hz), 8.52(1H, d, J=8.0Hz), 12.8(1H, br).

Example 66

Methyl 4-[2-({(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-[(isobutoxycarbonyl)amino]pentanoyl}-amino)ethyl]benzoate

The target compound was obtained in a similar manner to that of Example 36-2.

MS ((+)ESI) m/z : 560 $(M+Na)^+$.

Example 67

4-[2-({(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[(isobutoxycarbonyl)amino]pentanoyl}amino)-ethyl]benzoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 522 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 0.88(6H, d, J=7.0Hz), 1.28-1.87(5H, m), 2.76-2.83(2H, m), 2.92-3.01(2H, m), 3.21-3.43(2H, m), 3.70(2H, d, J=7.0Hz), 4.34-4.45(1H, m), 7.08(1H, t, J=5.5Hz), 7.31-7.52(4H, m), 7.62-7.86(5H, m), 8.14(1H, t, J=5.5Hz), 8.52(1H, d, J=8.0Hz), 12.8(1H, br).

Example 68-1

Methyl 3-[2-({(2S)-2-[(tert-butoxycarbonyl)amino]-5-[(1H-imidazol-1-ylcarbonyl)amino]pentanoyl}-

amino)phenyl]propanoate

To a solution of methyl 3-[2-[[(2S)-5-amino-2-[(tert-butoxycarbonyl)amino]pentanoyl]amino]phenyl]propanoate (6.36g) in tetrahydrofuran (60mL), was added 1,1'-carbonyldiimidazole (2.88g). The mixture was stirred at room temperature for 3 hours.

The solvent was removed by evaporation and the residue was dissolved in ethyl acetate (60mL). The solution was washed with brine (60mL×1) and dried over magnesium sulfate. Filtration followed by evaporation gave a crude solid (8.33g) which was chromatographed on silica gel (silica gel 500g, eluent: chloroform/methanol = 100/0 to 95/5) to give the target compound (7.88g) as a pale yellow solid.

Example 68-2

Methyl 3-{2-[((2S)-2-[(tert-butoxycarbonyl)amino]-5-{[(2-pyridinylmethoxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoate

To a solution of methyl 3-[2-[[(2S)-2-[(tert-butoxycarbonyl)amino]-5-[(1H-imidazol-1-ylcarbonyl)amino]pentanoyl]amino]phenyl]propanoate (500mg) obtained in Example 68-1 in acetonitrile (5.0mL), was added 2-pyridinemethanol (0.198mL). The mixture was refluxed for 17 hours. After cooling to room temperature, the solvent was removed by evaporation and the residue was chromatographed on silica gel (eluent: chloroform/methanol = 100/0 to 95/5) to give the target compound (226mg) as a light brown solid.

Example 68-3

Methyl 3-{2-[((2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-{[(2-pyridinylmethoxy)carbonyl]amino}-pentanoyl)amino]phenyl}propanoate

To a solution of methyl 3-[2-[[(2S)-2-[(tert-butoxycarbonyl)amino]-5-[[(2-pyridinylmethoxy)carbonyl]amino]pentanoyl]amino]-phenyl]propanoate (226mg) obtained in Example 68-2 in ethyl acetate (1mL), were added 4N hydrogen chloride in ethyl acetate (6mL) and methanol (1mL). The mixture was stirred at room temperature for 20 minutes. The solvent was removed by evaporation and the residue was dissolved in N,N-dimethylformamide (4mL). To the solution, were added 1-benzothiophene-2-carboxylic acid (83.8mg), 1-hydroxybenzotriazole (86.7mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.195mL). The mixture was stirred at room temperature for 3 hours.

The mixture was diluted with ethyl acetate (10mL), washed with water (10mL), saturated aqueous sodium hydrogencarbonate (10mL), water (10mL), and brine (10mL), and dried over magnesium sulfate. Filtration followed by evaporation gave a solid which was suspended in chloroform (1mL) and ethyl acetate (1mL). After stirring for 1 hour, the precipitates were collected by filtration, washed with ethyl acetate and dried under reduced pressure to give the target compound (123mg) as a pale orange solid.

MS ((+)ESI) m/z : 611 $(M+Na)^+$.

Example 69

Sodium 3-{2-[((2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-{[(2-pyridinylmethoxy)carbonyl]amino}-pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 59.

MS ((-)ESI) m/z : 573 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.48-1.73(2H, m), 1.82-2.09(2H, m), 2.21-2.37(2H, m), 2.63-2.91(2H, m), 3.03-3.23(2H, m), 4.60-4.72(1H, m), 5.06(2H, s), 6.95-7.49(8H, m), 7.74-8.04(5H, m), 8.51(1H, d, J=4.5Hz), 8.62(1H, s), 9.29(1H, d, J=8.0Hz), 12.5(1H, br).

Example 70-1
Methyl 3-{2-[((2S)-2-[(tert-butoxycarbonyl)amino]-5-{[(3-thienylmethoxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 68-2.

Example 70-2
Methyl 3-{2-[((2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-{[(3-thienylmethoxy)carbonyl]amino}-pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 68-3.

MS ((+)ESI) m/z : 616 $(M+Na)^+$.

Example 71
3-{2-[((2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-{[(3-thienylmethoxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 578 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.46-2.06(4H, m), 2.43-2.57(2H, m), 2.79-2.86(2H, m), 3.03-3.13(2H, m), 4.58-4.69(1H, m), 4.99(2H, s), 7.07-7.52(10H, m), 7.90-8.08(2H, m), 8.29(1H, s), 7.73(1H, d, J=7.5Hz), 9.60(1H, s), 12.2(1H, br).

Example 72-1

Methyl 3-{2-[((2S)-2-[(tert-butoxycarbonyl)amino]-5-{[(2-naphthylmethoxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 68-2.

Example 72-2

Methyl 3-{2-[((2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-{[(2-naphthylmethoxy)carbonyl]amino}-pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 68-3.

MS ((+)ESI) m/z : 660 $(M+Na)^+$.

Example 73

3-{2-[((2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-{[(2-naphthylmethoxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 622 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.44-2.05(4H, m), 2.47-2.54(2H, m), 2.75-2.86(2H, m), 3.04-3.16(2H, m), 4.61-4.71(1H, m), 5.19(2H, s), 7.00-7.54(10H, m), 7.82-8.05(6H, m), 8.30(1H, s), 8.95(1H, d, J=7.5Hz), 9.61(1H, s), 12.2(1H, br).

Example 74-1
Methyl 3-(2-{[(2S)-2-[(tert-butoxycarbonyl)amino]-5-({[(2-methylbenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 68-2.

Example 74-2
Methyl 3-(2-{[(2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-({[(2-methylbenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 68-3.

MS ((+)ESI) m/z : 624 $(M+Na)^+$.

Example 75
3-(2-{[(2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-({[(2-methylbenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 586 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.46-2.02(4H, m), 2.27(3H, s), 2.46-2.54(2H, m), 2.74-2.86(2H, m), 3.04-3.14(2H, m), 4.60-4.70(1H, m), 5.02(2H, s), 7.10-7.51(11H, m), 7.94-8.05(2H, m), 8.30(1H, s), 8.94(1H, d, J=7.5Hz), 9.60(1H, s), 12.2(1H, br).

Example 76-1
Methyl 3-(2-{[(2S)-2-[(tert-butoxycarbonyl)amino]-5-({[(3-methylbenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 68-2.

Example 76-2
Methyl 3-(2-{[(2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-({[(3-methylbenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 68-3.

MS ((+)ESI) m/z : 624 $(M+Na)^+$.

Example 77
3-(2-{[(2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-({[(3-methylbenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 586 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.47-2.00(4H, m), 2.28(3H, s), 2.46-2.54(2H, m), 2.78-2.86(2H, m), 3.05-3.14(2H,

m), 4.60-4.70(1H, m), 4.97(2H, s), 7.14-7.48(11H, m), 7.94-8.05(2H, m), 8.30(1H, s), 8.94(1H, d, J=7.5Hz), 9.61(1H, s), 12.2(1H, br).

Example 78

Methyl 3-[2-({(2S)-5-({[(2-chlorobenzyl)oxy]-carbonyl}amino)-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 639 $(M+Na)^+$.

Example 79

3-[2-({(2S)-5-({[(2-Chlorobenzyl)oxy]carbonyl}-amino)-2-[(2-quinolinylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 601 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.52-1.67(2H, m), 1.86-2.07(2H, m), 2.45-2.54(2H, m), 2.79-2.87(2H, m), 3.05-3.14(2H, m), 4.80-4.90(1H, m), 5.06(2H, s), 7.15-7.57(9H, m), 7.70-7.93(2H, m), 8.09-8.22(3H, m), 8.61(1H, d, J=8.5Hz), 8.91(1H, d, J=8.5Hz), 9.75(1H, br-s), 12.2(1H, br-s).

Example 80

Benzyl {(4S)-4-[(1-benzofuran-2-ylcarbonyl)amino]-5-[(5-cyanopentyl)amino]-5-oxopentyl}carbamate

The target compound was obtained in a similar

manner to that of Example 42-1.

Example 81

Benzyl ((4S)-4-[(1-benzofuran-2-ylcarbonyl)amino]-5-oxo-5-{[5-(2H-tetrazol-5-yl)pentyl]amino}-pentyl)carbamate

To a solution of benzyl [(4S)-4-[(1-benzofuran-2-ylcarbonyl)amino]-5-[(5-cyanopentyl)amino]-5-oxopentyl]carbamate (300mg) obtained in Example 80 in 1-methyl-2-pyrrolidinone (6mL), were added sodium azide (193mg) and triethylamine hydrochloride (193mg). The mixture was stirred at 140℃ for 20 hours.

After cooling to room temperature, the mixture was quenched by the addition of 1N hydrochloric acid (20mL) and extracted with ethyl acetate (20mL×1, 10mL×1). The extracts were combined and washed with water (20mL×2) and brine (20mL×1), and dried over magnesium sulfate. Filtration followed by evaporation gave a crude product (280mg) which was chromatographed on silica gel (eluent: chloroform/methanol = 99/1 to 95/5) to give the target compound (155mg) as a yellow solid.

MS ((+)ESI) m/z : 570 $(M+Na)^+$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.23-1.84(10H, m), 2.83-3.13(6H, m), 4.38-4.49(1H, m), 5.01(2H, s), 7.26-7.52(8H, m), 7.64-7.81(3H, m), 8.06(1H, t, J=5.5Hz), 8.52(1H, d, J=8.0Hz).

Example 82-1

Ethyl 4-{2-[((2S)-2-amino-5-{[(benzyloxy)-carbonyl]amino}pentanoyl)amino]phenyl}butanoate hydrochloride

To a solution of ethyl 4-[2-[[(2S)-5-[[(benzyloxy)carbonyl]amino]-2-[(tert-butoxy-carbonyl)amino]pentanoyl]amino]phenyl] butanoate (518mg) in 1,4-dioxane (1mL), was added 4N hydrogen chloride in 1,4-dioxane (4mL). The mixture was stirred at room temperature for 2 hours. The solvent was removed by evaporation to give the target compound (476mg) as a pale yellow solid.

Example 82-2
Ethyl 4-{2-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}-pentanoyl)amino]phenyl}butanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 635 $(M+Na)^+$.

Example 83
4-{2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}pentanoyl)-amino]phenyl}butanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 583 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.53-1.95(6H, m), 2.18-2.26(2H, m), 2.55-2.63(2H, m), 3.05-3.14(2H, m), 3.99(3H, s), 4.57-4.68(1H, m), 5.02(2H, s), 7.07-7.40(13H, m), 7.53(1H, d, J=8.0Hz), 7.66(1H, d, J=8.0Hz), 8.61(1H, d, J=7.5Hz), 9.44(1H, br-s), 12.1(1H, br).

Example 84
Ethyl 4-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)-phenyl]butanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 633 $(M+Na)^+$.

Example 85
4-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)phenyl]-butanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 581 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.51-1.78(4H, m), 1.88-2.03(2H, m), 2.17-2.24(2H, m), 2.55-2.62(2H, m), 4.80-4.90(1H, m), 4.99(2H, s), 7.15-7.42(10H, m), 7.70-7.78(1H, m), 7.85-7.93(1H, m), 8.09-8.22(2H, m), 8.61(1H, d, J=8.0Hz), 8.92(1H, d, J=8.0Hz), 9.65(1H, br-s), 12.1(1H, br).

Example 86-1
Methyl 3-(2-{[(2S)-2-[(tert-butoxycarbonyl)amino]-5-({[(4-methylbenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

In a reaction vessel, was added a solution of methyl 3-[2-[[(2S)-2-[(tert-butoxycarbonyl)amino]-5-[(1H-imidazol-1-ylcarbonyl)amino]pentanoyl]amino]-phenyl]propanoate (500mg) and (4-methylphenyl)-

methanol (251mg) in acetonitrile (5mL). The vessel was placed in a microwave. The irradiation was adjusted to keep the temperature 140℃ and the reaction was performed for 2 hours. After cooling to room temperature, the solvent was removed by evaporation, and the residue was chromatographed on silica gel (eluent: hexane/ethyl acetate = 2/1 to 1/1) to give the target compound (376mg) as a white solid.

MS ((+)ESI) m/z : 564 $(M+Na)^+$.

Example 86-2
Methyl 3-(2-{[(2S)-2-amino-5-({[(4-methylbenzyl)-oxy]carbonyl}amino)pentanoyl]amino}phenyl)-propanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

Example 86-3
Methyl 3-{2-[((2S)-5-({[(4-methylbenzyl)oxy]-carbonyl}amino)-2-{[(1-methyl-1H-indol-2-yl)-carbonyl]amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 621 $(M+Na)^+$.

Example 87
3-{2-[((2S)-5-({[(4-Methylbenzyl)oxy]carbonyl}-amino)-2-{[(1-methyl-1H-indol-2-yl)carbonyl]-amino}pentanoyl)amino]phenyl}propanoic acid

The target compound was obtained in a similar

manner to that of Example 28.

MS ((-)ESI) m/z : 583 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.52-1.69(2H, m), 1.81-1.95(2H, m), 2.27(3H, s), 2.47-2.54(2H, m), 2.79-2.86(2H, m), 3.03-3.13(2H, m), 3.98(3H, s), 4.55-4.66(1H, m), 4.96(2H, s), 7.07-7.37(12H, m), 7.53(1H, d, J=8.0Hz), 7.65(1H, d, J=7.5Hz), 8.62(1H, d, J=7.5Hz), 9.56(1H, br-s), 12.1(1H, br).

Example 88
Methyl 3-[2-({(2S)-5-({[(4-methylbenzyl)oxy]-carbonyl}amino)-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 619 $(M+Na)^+$.

Example 89
3-[2-({(2S)-5-({[(4-Methylbenzyl)oxy]carbonyl}-amino)-2-[(2-quinolinylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 581 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.56-1.66(2H, m), 1.85-2.06(2H, m), 2.25(3H, s), 2.45-2.51(2H, m), 2.80-2.87(2H, m), 3.04-3.13(2H, m), 4.81-4.87(1H, m), 4.94(2H, s), 7.10-7.40(9H, m), 7.71-7.93(2H, m), 8.09-8.23(3H, m), 8.61(1H, d, J=8.5Hz), 8.92(1H, d, J=8.5Hz), 9.76(1H, br-s), 12.2(1H, br).

Example 90-1
Methyl 3-{2-[((2S)-2-[(tert-butoxycarbonyl)amino]-5-{[(3-furylmethoxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 86-1.

MS ((+)ESI) m/z : 540 $(M+Na)^+$.

Example 90-2
Methyl 3-{2-[((2S)-2-amino-5-{[(3-furylmethoxy)-carbonyl]amino}pentanoyl)amino]phenyl}propanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

Example 90-3
Methyl 3-{2-[((2S)-5-{[(3-furylmethoxy)carbonyl]-amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]-amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 597 $(M+Na)^+$.

Example 91
3-{2-[((2S)-5-{[(3-Furylmethoxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}-pentanoyl)amino]phenyl}propanoic acid

The target compound was obtained in a similar

manner to that of Example 28.

MS ((-)ESI) m/z : 559 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.51-1.69(2H, m), 1.81-1.94(2H, m), 2.46-2.54(2H, m), 2.79-2.86(2H, m), 3.03-3.12(2H, m), 3.98(3H, s), 4.55-4.65(1H, m), 4.86(2H, s), 6.48(1H, d, J=1.5Hz), 7.07-7.37(8H, m), 7.51-7.68(4H, m), 8.62(1H, d, J=7.5Hz), 9.55(1H, br-s), 12.1(1H, br).

Example 92

Methyl 3-[2-({(2S)-5-{[(3-furylmethoxy)carbonyl]-amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 595 $(M+Na)^+$.

Example 93

3-[2-({(2S)-5-{[(3-Furylmethoxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 557 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.51-1.65(2H, m), 1.85-2.06(2H, m), 2.45-2.53(2H, m), 2.79-2.87(2H, m), 3.03-3.11(2H, m), 4.79-4.90(3H, m), 6.46(1H, s), 7.11-7.39(5H, m), 7.59-7.90(4H, m), 8.09-8.22(3H, m), 8.61(1H, d, J=8.5Hz), 8.91(1H, d, J=8.0Hz), 9.75(1H, br-s), 12.1(1H, br).

Example 94-1
Methyl 3-{2-[((2S)-2-[(tert-butoxycarbonyl)amino]-5-{[(3-pyridinylmethoxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 86-1.

MS ((+)ESI) m/z : 551 $(M+Na)^+$.

Example 94-2
Methyl 3-{2-[((2S)-2-amino-5-{[(3-pyridinyl-methoxy)carbonyl]amino}pentanoyl)amino]phenyl}-propanoate dihydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

Example 94-3
Methyl 3-{2-[((2S)-2-{[(1-methyl-1H-indol-2-yl)-carbonyl]amino}-5-{[(3-pyridinylmethoxy)carbonyl]-amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 608 $(M+Na)^+$.

Example 95
Sodium 3-{2-[((2S)-2-{[(1-methyl-1H-indol-2-yl)-carbonyl]amino}-5-{[(3-pyridinylmethoxy)carbonyl]-amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar

manner to that of Example 59.

MS ((-)ESI) m/z : 570 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.50-1.68(2H, m), 1.81-2.04(2H, m), 2.25-2.30(2H, m), 2.73-2.78(2H, m), 3.07-3.16(2H, m), 3.99(3H, s), 4.61-4.72(1H, m), 5.04(2H, s), 6.97-7.15(4H, m), 7.23-7.65(6H, m), 7.75-7.85(3H, m), 8.50(1H, dd, J=1.5, 4.5Hz), 8.57(1H, d, J=2.0Hz), 8.74(1H, d, J=8.5Hz).

Example 96
Methyl 3-[2-({(2S)-5-{[(3-pyridinylmethoxy)-carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 606 $(M+Na)^+$.

Example 97
Sodium 3-[2-({(2S)-5-{[(3-pyridinylmethoxy)-carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 59.

MS ((-)ESI) m/z : 568 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.46-1.68(2H, m), 1.85-2.13(2H, m), 2.28-2.31(2H, m), 2.64-2.86(2H, m), 3.10-3.18(2H, m), 4.82-4.92(1H, m), 5.03(2H, s), 6.97-7.18(3H, m), 7.33-7.39(1H, m), 7.70-7.94(5H, m), 8.11(1H, d, J=8.0Hz), 8.21(1H, d, J=8.5Hz), 8.48-8.63(3H, m), 9.00(1H, d, J=8.5Hz), 13.0(1H,

br-s)..

Example 98-1
Methyl 3-{2-[((2S)-2-[(tert-butoxycarbonyl)amino]-5-{[(4-pyridinylmethoxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 86-1.

MS ((+)ESI) m/z : 551 $(M+Na)^+$.

Example 98-2
Methyl 3-{2-[((2S)-2-amino-5-{[(4-pyridinyl-methoxy)carbonyl]amino}pentanoyl)amino]phenyl}-propanoate dihydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

Example 98-3
Methyl 3-[2-({(2S)-5-{[(4-pyridinylmethoxy)-carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 606 $(M+Na)^+$.

Example 99
Sodium 3-[2-({(2S)-5-{[(4-pyridinylmethoxy)-carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 59.

MS ((-)ESI) m/z : 568 $(M-Na)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.45-1.73(2H, m), 1.86-2.18(2H, m), 2.26-2.36(2H, m), 2.70-2.84(2H, m), 3.12-3.21(2H, m), 4.84-4.95(1H, m), 5.04(2H, s), 7.01-7.18(3H, m), 7.31(2H, d, J=5.5Hz), 7.70-8.13(5H, m), 8.22(2H, d, J=8.5Hz), 8.51(2H, d, J=6.0Hz), 8.61(1H, d, J= 8.5Hz), 9.01(1H, d, J=8.5Hz), 13.0(1H, br-s).

Example 100-1

Methyl 3-(2-{[(2S)-2-[(tert-butoxycarbonyl)-amino]-5-({[(3-chlorobenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 86-1.

MS ((+)ESI) m/z : 584 $(M+Na)^+$.

Example 100-2

Methyl 3-(2-{[(2S)-2-amino-5-({[(3-chlorobenzyl)-oxy]carbonyl}amino)pentanoyl]amino}phenyl)-propanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

Example 100-3

Methyl 3-{2-[((2S)-5-({[(3-chlorobenzyl)oxy]-carbonyl}amino)-2-{[(1-methyl-1H-indol-2-yl)-carbonyl]amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar

manner to that of Example 27-3.

MS ((+)ESI) m/z : 641 $(M+Na)^+$.

Example 101

3-{2-[((2S)-5-({[(3-Chlorobenzyl)oxy]carbonyl}-amino)-2-{[(1-methyl-1H-indol-2-yl)carbonyl]-amino}pentanoyl)amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 603 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.50-1.70(2H, m), 1.83-1.96(2H, m), 2.47-2.55(2H, m), 2.79-2.87(2H, m), 3.05-3.14(2H, m), 4.01(3H, s), 4.56-4.66(1H, m), 5.02(2H, s), 7.07-7.41(12H, m), 7.53(1H, d, J=8.0Hz), 7.65(1H, d, J=8.0Hz), 8.63(1H, d, J=8.0Hz), 9.55(1H, br-s), 12.1(1H, br).

Example 102

Methyl 3-[2-({(2S)-5-({[(3-chlorobenzyl)oxy]-carbonyl}amino)-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 639 $(M+Na)^+$.

Example 103

3-[2-({(2S)-5-({[(3-Chlorobenzyl)oxy]carbonyl}-amino)-2-[(2-quinolinylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 601 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.53-1.68(2H, m), 1.87-2.08(2H, m), 2.46-2.55(2H, m), 2.81-2.88(2H, m), 3.05-3.14(2H, m), 4.82-4.92(1H, m), 5.00(2H, s), 7.13-7.38(9H, m), 7.74(1H, t, J=7.0Hz), 7.89(1H, t, J=7.0Hz), 8.09-8.22(3H, m), 8.61(1H, d, J=8.5Hz), 8.92(1H, d, J=8.0Hz), 9.76(1H, br-s), 12.2(1H, br).

Example 104-1

Methyl 3-(2-{[(2S)-2-[(tert-butoxycarbonyl)-amino]-5-({[(4-chlorobenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 86-1.

MS ((+)ESI) m/z : 584 $(M+Na)^+$.

Example 104-2

Methyl 3-(2-{[(2S)-2-amino-5-({[(4-chlorobenzyl)-oxy]carbonyl}amino)pentanoyl]amino}phenyl)-propanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

Example 104-3

Methyl 3-{2-[((2S)-5-({[(4-chlorobenzyl)oxy]-carbonyl}amino)-2-{[(1-methyl-1H-indol-2-yl)-carbonyl]amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar

manner to that of Example 27-3.

MS ((+)ESI) m/z : 641 $(M+Na)^+$.

Example 105

3-{2-[((2S)-5-({[(4-Chlorobenzyl)oxy]carbonyl}-amino)-2-{[(1-methyl-1H-indol-2-yl)carbonyl]-amino}pentanoyl)amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 603 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.53-1.70(2H, m), 1.82-1.96(2H, m), 2.47-2.55(2H, m), 2.79-2.87(2H, m), 3.04-3.14(2H, m), 3.98(3H, s), 4.56-4.67(1H, m), 5.01(2H, s), 7.07-7.44(12H, m), 7.53(1H, d, J=8.5Hz), 7.66(1H, d, J=7.5Hz), 8.62(1H, d, J=7.5Hz), 9.55(1H, br-s), 12.1(1H, br).

Example 106

Methyl 3-[2-({(2S)-5-({[(4-chlorobenzyl)oxy]-carbonyl}amino)-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 639 $(M+Na)^+$.

Example 107

3-[2-({(2S)-5-({[(4-Chlorobenzyl)oxy]carbonyl}-amino)-2-[(2-quinolinylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 601 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.52-1.67(2H, m), 1.86-2.07(2H, m), 2.46-2.54(2H, m), 2.80-2.88(2H, m), 3.04-3.14(2H, m), 4.81-4.91(1H, m), 4.99(2H, s), 7.16-7.40(9H, m), 7.70-7.93(2H, m), 8.09-8.23(3H, m), 8.61(1H, d, J=8.5Hz), 8.92(1H, d, J=8.0Hz), 9.75(1H, br-s), 12.2(1H, br).

Example 108-1
Methyl 3-(2-{[(2S)-2-[(tert-butoxycarbonyl)-amino]-5-({[(2-methylbenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 86-1.

Example 108-2
Methyl 3-(2-{[(2S)-2-amino-5-({[(2-methylbenzyl)-oxy]carbonyl}amino)pentanoyl]amino}phenyl)-propanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

Example 108-3
Methyl 3-{2-[((2S)-5-({[(2-methylbenzyl)oxy]-carbonyl}amino)-2-{[(1-methyl-1H-indol-2-yl)-carbonyl]amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 621 $(M+Na)^+$.

Example 109

3-{2-[((2S)-5-({[(2-Methylbenzyl)oxy]carbonyl}-amino)-2-{[(1-methyl-1H-indol-2-yl)carbonyl]-amino}pentanoyl)amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 583 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.52-1.69(2H, m), 1.81-1.95(2H, m), 2.27(3H, s), 2.46-2.54(2H, m), 2.79-2.86(2H, m), 3.04-3.13(2H, m), 3.98(3H, s), 4.55-4.66(1H, m), 5.01(2H, s), 7.07-7.36(12H, m), 7.53(1H, d, J=8.0Hz), 7.65(1H, d, J=8.0Hz), 8.62(1H, d, J=7.5Hz), 9.56(1H, br-s), 12.1(1H, br).

Example 110

Methyl 3-[2-({(2S)-5-({[(2-methylbenzyl)oxy]-carbonyl}amino)-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 619 $(M+Na)^+$.

Example 111

3-[2-({(2S)-5-({[(2-Methylbenzyl)oxy]carbonyl}-amino)-2-[(2-quinolinylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 581 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.51-1.66(2H, m), 1.86-2.07(2H, m), 2.25(3H, s), 2.45-2.53(2H, m), 2.80-2.87(2H, m), 3.04-3.13(2H, m), 4.80-4.91(1H, m), 4.99(2H, s), 7.12-7.40(9H, m), 7.70-7.93(2H, m), 8.09-8.22(3H, m), 8.61(1H, d, J=8.5Hz), 8.91(1H, d, J=8.5Hz), 9.76(1H, br-s), 12.2(1H, br).

Example 112-1

Methyl 3-(2-{[(2S)-2-[(tert-butoxycarbonyl)-amino]-5-({[(3-methylbenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 86-1.

Example 112-2

Methyl 3-(2-{[(2S)-2-amino-5-({[(3-methylbenzyl)-oxy]carbonyl}amino)pentanoyl]amino}phenyl)-propanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

Example 112-3

Methyl 3-{2-[((2S)-5-({[(3-methylbenzyl)oxy]-carbonyl}amino)-2-{[(1-methyl-1H-indol-2-yl)-carbonyl]amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 621 $(M+Na)^+$.

Example 113
3-{2-[((2S)-5-({[(3-Methylbenzyl)oxy]carbonyl}-amino)-2-{[(1-methyl-1H-indol-2-yl)carbonyl]-amino}pentanoyl)amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 583 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.53-1.70(2H, m), 1.82-1.96(2H, m), 2.28(3H, s), 2.47-2.54(2H, m), 2.79-2.87(2H, m), 3.05-3.14(2H, m), 3.98(3H, s), 4.56-4.66(1H, m), 4.97(2H, s), 7.07-7.36(12H, m), 7.53(1H, d, J=8.5Hz), 7.65(1H, d, J=8.5Hz), 8.63(1H, d, J=7.5Hz), 9.56(1H, br-s), 12.2(1H, br).

Example 114
Methyl 3-[2-({(2S)-5-({[(3-methylbenzyl)oxy]-carbonyl}amino)-2-[(2-quinolinylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 619 $(M+Na)^+$.

Example 115
3-[2-({(2S)-5-({[(3-Methylbenzyl)oxy]carbonyl}-amino)-2-[(2-quinolinylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 581 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.54-1.67(2H, m), 1.90-2.04(2H, m), 2.27(3H, s), 2.46-2.54(2H, m), 2.81-2.88(2H, m), 3.05-3.14(2H, m), 4.81-4.92(1H, m), 4.95(2H, s), 7.12-7.39(9H, m), 7.71-7.93(2H, m), 8.09-8.23(3H, m), 8.61(1H, d, J=8.5Hz), 8.92(1H, d, J=8.0Hz), 9.76(1H, br-s), 12.2(1H, br).

Example 116-1
Methyl 3-[({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-methyl]benzoate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 536 $(M+Na)^+$.

Example 116-2
Methyl 3-{[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]methyl}benzoate hydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

MS ((+)ESI) m/z : 436 $(M+Na)^+$.

Example 116-3
Methyl 3-{[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}-pentanoyl)amino]methyl}benzoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 593 $(M+Na)^+$.

Example 117
3-{[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}pentanoyl)-amino]methyl}benzoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 555 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.44-1.87(4H, m), 3.00-3.09(2H, m), 3.97(3H, s), 4.37(2H, d, J=6.0Hz), 4.42-4.50(1H, m), 5.00(2H, s), 7.08-7.89(15H, m), 8.50-8.60(2H, m), 12.9(1H, br).

Example 118
Methyl 3-[({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)-methyl]benzoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 591 $(M+Na)^+$.

Example 119
3-[({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)methyl]-benzoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 553 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.45-1.59(2H, m), 1.80-1.95(2H, m), 3.01-3.11(2H, m), 4.42(2H, d, J=5.5Hz), 4.62-4.72(1H, m), 5.00(2H, s), 7.25-7.57(7H, m), 7.71-7.93(4H, m), 8.08-8.22(3H, m), 8.60(1H, d, J=8.5Hz), 8.80-8.89(2H, m), 12.9(1H, br).

Example 120-1
Methyl {3-[({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-methyl]phenyl}acetate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 550 $(M+Na)^+$.

Example 120-2
Methyl (3-{[((2S)-2-amino-5-{[(benzyloxy)-carbonyl]amino}pentanoyl)amino]methyl}phenyl)-acetate hydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

MS ((+)ESI) m/z : 428 $(M+H)^+$.

Example 120-3
Methyl (3-{[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}-pentanoyl)amino]methyl}phenyl)acetate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 607 $(M+Na)^+$.

Example 121
(3-{[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}pentanoyl)-amino]methyl}phenyl)acetic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 569 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.40-1.88(4H, m), 3.00-3.09(2H, m), 3.53(2H, s), 3.97(3H, s), 4.30(2H, d, J=6.0Hz), 4.39-4.50(1H, m), 5.00(2H, s), 7.06-7.66(15H, m), 8.50(2H, d, J=5.0Hz), 12.3(1H, br).

Example 122
Methyl {3-[({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)-methyl]phenyl}acetate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 605 $(M+Na)^+$.

Example 123
{3-[({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)methyl]-phenyl}acetic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 567 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.43-1.57(2H, m),

1.77-1.92(2H, m), 3.00-3.09(2H, m), 3.54(2H, s), 4.33(2H, d, J=5.5Hz), 4.59-4.70(1H, m), 4.99(2H, s), 7.12-7.32(10H, m), 7.70-7.93(2H, m), 8.11(1H, d, J=7.5 Hz), 8.19(2H, d, J=8.5Hz), 8.60(1H, d, J=8.5Hz), 8.72-8.86(2H, m), 12.3(1H, br).

Example 124-1

Ethyl {2-[({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-methyl]phenyl}acetate

The target compound was obtained in a similar manner to that of Example 42-1.

MS ((+)ESI) m/z : 564 $(M+Na)^+$.

Example 124-2

Ethyl (2-{[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]methyl}phenyl)acetate hydrochloride

The target compound was obtained in a similar manner to that of Example 82-1.

MS ((+)ESI) m/z : 442 $(M+H)^+$.

Example 124-3

Ethyl (2-{[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}-pentanoyl)amino]methyl}phenyl)acetate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 621 $(M+Na)^+$.

Example 125
(2-{[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}pentanoyl)-amino]methyl}phenyl)acetic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 569 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.43-1.61(2H, m), 1.71-1.85(2H, m), 3.00-3.09(2H, m), 3.66(2H, s), 3.97(3H, s), 4.31(2H, d, J=5.5Hz), 4.39-4.49(1H, m), 5.00(2H, s), 7.07-7.33(13H, m), 7.53(1H, d, J=8.5Hz), 7.64(1H, d, J=8.0Hz), 8.40(1H, t, J=6.0Hz), 8.50(1H, d, J=8.0Hz), 12.4(1H, br).

Example 126
Ethyl {2-[({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)-methyl]phenyl}acetate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 619 $(M+Na)^+$.

Example 127
{2-[({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)methyl]-phenyl}acetic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 567 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.41-1.56(2H, m), 1.76-1.91(2H, m), 2.98-3.08(2H, m), 3.67(2H, s), 4.34(2H, d, J=6.0Hz), 4.58-4.69(1H, m), 4.98(2H, s), 7.20-7.32(10H, m), 7.70-7.93(2H, m), 8.10(1H, d, J=7.5Hz), 8.18(2H, d, J=8.5Hz), 8.58-8.68(2H, m), 8.83(1H, d, J=8.5Hz), 12.4(1H, br).

Example 128

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]hexanoate

To a solution of sodium 6-[[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[[(benzyloxy)-carbonyl]amino]pentanoyl]amino]hexanoate (150mg) in N,N-dimethylacetamide (1.5mL), was added 4-(bromomethyl)-5-methyl-1,3-dioxol-2-one (37.5μL). The mixture was stirred at room temperature for 20 hours. The mixture was diluted with water (10mL) and extracted with ethyl acetate (10mL). The organic layer was washed with water (10mL×2) and brine (10mL), and dried over magnesium sulfate. Filtration followed by evaporation gave the target compound (93mg) as a white solid.

MS ((+)ESI) m/z : 658 $(M+Na)^+$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.17-1.82(10H, m), 2.14(3H, s), 2.33(2H, t, J=7.0Hz), 2.97-3.10(4H, m), 4.35-4.46(1H, m), 4.93(2H, s), 5.00(2H, s), 7.22-7.52(8H, m), 7.63(1H, s), 7.68(1H, d, J=8.5Hz), 7.78(1H, d, J=7.0Hz), 8.03(1H, t, J=5.5Hz), 8.50(1H, d, J=8.0Hz).

Example 129

[(2,2-Dimethylpropanoyl)oxy]methyl 6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)-carbonyl]amino}pentanoyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 128.

MS ((+)ESI) m/z : 660 $(M+Na)^+$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.13(9H, s), 1.20-1.80(10H, m), 2.34(2H, t, J=7.0Hz), 2.96-3.10(4H, m), 4.35-4.46(1H, m), 5.00(2H, s), 5.68(2H, s), 7.24-7.52(8H, m), 7.62(1H, s), 7.69(1H, d, J=8.5Hz), 7.78(1H, d, J=7.0Hz), 8.03(1H, t, J=5.5Hz), 8.50(1H, d, J=8.0Hz).

Example 130
1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-{[(benzyl-oxy)carbonyl]amino}pentanoyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 128.

MS ((+)ESI) m/z : 716 $(M+Na)^+$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.16-1.87(23H, m), 2.31(2H, t, J=7.0Hz), 2.96-3.09(4H, m), 4.33-4.63(2H, m), 5.00(2H, s), 6.62(1H, q, J=5.0Hz), 7.24-7.52(8H, m), 7.62(1H, s), 7.69(1H, d, J=8.5Hz), 7.78(1H, d, J=7.5Hz), 8.03(1H, t, J=5.5Hz), 8.50(1H, d, J=8.0Hz).

Example 131
Methyl 3-{2-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-3-yl)carbonyl]amino}-pentanoyl)amino]phenyl}propanate

To a solution of methyl 3-[2-[[(2S)-2-amino-5-[[(benzyloxy)carbonyl]amino]pentanoyl]-amino]phenyl]propanoate hydrochloride (208mg) and 1-hydroxybenzotriazole (160mg) in N,N-dimethylformamide (5.0mL), was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (184mg) at 5℃ under nitrogen. The mixture was stirred at room temperature for 12 hours.

The resulting mixture was poured into water and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate three times and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 1 : 1 to 1 : 2) to give the target compound (357mg).

MS ((+)ESI) m/z : 607 $(M+Na)^+$.

Example 132

3-{2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-3-yl)carbonyl]amino}pentanoyl)-amino]phenyl}propanoic acid

To a solution of methyl 3-[2-[[(2S)-5-[[(benzyloxy)carbonyl]amino]-2-[[(1-methyl-1H-indol-3-yl)carbonyl]amino]pentanoyl]-amino]phenyl]propanoic acid (355mg) obtained in Example 131 in 1,4-dioxane (10mL), was added 1N sodium hydroxide (1.82mL) at room temperature. The mixture was stirred at 45℃ for 2.5 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with a mixture of chloroform and methanol (5 : 1). The organic layer

was dried over anhydrous magnesium sulfate, evaporated, and dried in vacuo to give the target compound (373mg).

MS ((-)ESI) m/z : 569 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.5-1.95(4H, m), 2.4-2.5(2H, m), 2.75-2.9(2H, m), 3.0-3.15(2H, m), 3.84(3H, s), 4.6-4.8(1H, m), 5.00(2H, s), 7.05-7.55(11H, m), 7.95-8.05(1H, m), 8.1-8.1(2H, m).

Example 133

Methyl 3-{2-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indazol-3-yl)carbonyl]amino}-pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 608 $(M+Na)^+$.

Example 134

3-{2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indazol-3-yl)carbonyl]amino}pentanoyl)-amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 570 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.45-1.65(2H, m), 1.85-2.0(2H, m), 2.4-2.5(2H, m), 2.75-2.9(2H, m), 3.0-3.15(2H, m), 4.15(3H, s), 4.7-4.95(1H, m), 4.99(2H, s), 7.1-7.55(10H, m), 7.7-7.8(1H, m), 8.1-8.5(2H, m).

Example 135

Methyl 3-{2-[((2S)-5-{[(benzyloxy)carbonyl]amino}-

2-{[(8-methylimidazo[1,2-a]pyridin-2-yl)carbonyl]-amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 608 $(M+Na)^+$.

Example 136

3-{2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(8-methylimidazo[1,2-a]pyridin-2-yl)carbonyl]amino}-pentanoyl)amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 570 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.5-2.0(4H, m), 2.4-2.5(2H, m), 2.58(3H, s), 2.75-2.9(2H, m), 3.0-3.2(2H, m), 4.75-4.9(1H, m), 5.00(2H, s), 7.1-7.55(10H, m), 8.6-8.9(3H, m).

Example 137

Methyl 3-(2-{[(2S)-5-{[(benzyloxy)carbonyl]amino}-2-(2-naphthoylamino)pentanoyl]amino}phenyl)-propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 604 $(M+Na)^+$.

Example 138

3-(2-{[(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-(2-naphthoylamino)pentanoyl]amino}phenyl)propanoic

acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 566 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.5-1.75(2H, m), 1.8-2.0(2H, m), 2.45-2.6(2H, m), 2.75-2.9(2H, m), 3.05-3.2(2H, m), 4.6-4.8(1H, m), 5.01(2H, s), 7.1-7.45(9H, m), 7.55-7.7(2H, m), 7.9-8.1(4H, m), 8.56(1H, s).

Example 139
Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(3-quinolinylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 605 $(M+Na)^+$.

Example 140
3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(3-quinolinylcarbonyl)amino]pentanoyl}amino)phenyl]-propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 567 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.5-2.1(4H, m), 2.35-2.6(2H, m), 2.7-2.9(2H, m), 2.95-3.2(2H, m), 4.6-4.8(1H, m), 5.01(2H, s), 7.05-7.5(9H, m), 7.65-7.75(1H, m), 7.8-7.95(1H, m), 8.05-8.2(2H, m), 9.04(1H, s), 9.35(1H, m).

Example 141
Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(3-isoquinolinylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 605 $(M+Na)^+$.

Example 142
3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(3-isoquinolinylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 567 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.5-1.7(2H, m), 1.8-2.05(2H, m), 2.4-2.55(2H, m), 2.75-2.9(2H, m), 3.0-3.2(2H, m), 4.8-4.95(1H, m), 4.98(2H, s), 7.1-7.45(9H, m), 7.75-7.95(2H, m), 8.15-8.35(2H, m), 8.61(1H, s), 9.79(1H, s).

Example 143
Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-quinoxalinylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 606 $(M+Na)^+$.

Example 144
3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(2-quinoxalinylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 568 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.5-1.7(2H, m), 1.85-2.1(2H, m), 2.4-2.5(2H, m), 2.75-2.9(2H, m), 3.05-3.2(2H, m), 4.75-4.9(1H, m), 4.99(2H, s), 7.1-7.45(9H, m), 7.95-8.05(2H, m), 8.2-8.35(2H, m), 9.51(1H, s).

Example 145
Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(4-quinolinylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 605 $(M+Na)^+$.

Example 146
3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(4-quinolinylcarbonyl)amino]pentanoyl}amino)phenyl]-propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 567 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.55-2.0(4H, m), 2.45-2.6(2H, m),

2.8-2.95(2H, m), 3.05-3.2(2H, m), 4.65-4.8(1H, m), 5.01(2H, s), 7.1-7.4(9H, m), 7.55-7.7(2H, m), 7.75-7.9(1H, m), 8.05-8.1(1H, m), 8.2-8.25(1H, m), 8.95-9.0(1H, m).

Example 147

Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(1-isoquinolinylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 605 $(M+Na)^+$.

Example 148

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(1-isoquinolinylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 567 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.5-2.05(4H, m), 2.4-2.55(2H, m), 2.75-2.9(2H, m), 3.05-3.2(2H, m), 4.7-4.9(1H, m), 4.99(2H, s), 7.1-7.45(9H, m), 7.7-7.9(2H, m), 8.0-8.1(2H, m), 8.55-8.6(1H, m), 8.95-9.05(1H, m).

Example 149

Methyl 3-{2-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[5-(4-chlorophenyl)-2-furoyl]amino}pentanoyl)-amino]phenyl}propanoate

The target compound was obtained in a similar

manner to that of Example 131.

MS ((+)ESI) m/z : 654, 656 $(M+Na)^+$.

Example 150

3-{2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[5-(4-chlorophenyl)-2-furoyl]amino}pentanoyl)amino]-phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 616, 618 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.5-2.0(4H, m), 2.45-2.55(2H, m), 2.75-2.9(2H, m), 3.0-3.2(2H, m), 4.6-4.75(1H, m), 7.1-7.4(11H, m), 7.5-7.6(2H, m), 7.9-8.0(2H, m).

Example 151

Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-biphenylylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 630 $(M+Na)^+$.

Example 152

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(2-biphenylylcarbonyl)amino]pentanoyl}amino)phenyl]-propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 592 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.2-1.8(4H, m), 2.4-2.55(2H, m), 2.7-2.85(2H, m), 2.9-3.05(2H, m), 4.35-4.5(1H, m), 5.02(2H, s), 7.1-7.6(18H, m).

Example 153
Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(4-phenoxybenzoyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 646 $(M+Na)^+$.

Example 154
3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(4-phenoxybenzoyl)amino]pentanoyl}amino)phenyl]-propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 608 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.45-1.7(2H, m), 1.75-1.95(2H, m), 2.4-2.6(2H, m), 2.75-2.9(2H, m), 3.0-3.2(2H, m), 4.5-4.7(1H, m), 5.00(2H, s), 7.0-7.5(16H, m), 7.9-8.0(2H, m).

Example 155
Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(3,4-dimethoxybenzoyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar

manner to that of Example 131.

MS ((+)ESI) m/z : 614 $(M+Na)^+$.

Example 156

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(3,4-dimethoxybenzoyl)amino]pentanoyl}amino)-phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 576 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.45-1.7(2H, m), 1.75-2.0(2H, m), 2.4-2.55(2H, m), 2.75-2.9(2H, m), 3.0-3.2(2H, m), 3.81(6H, s), 4.55-4.75(1H, m), 5.00(2H, s), 7.0-7.45(10H, m), 7.5-7.65(2H, m).

Example 157

Methyl 3-{2-[((2S)-5-{[(benzyloxy)carbonyl]-amino}-2-{[(6-methyl-2-pyridinyl)carbonyl]amino}-pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 569 $(M+Na)^+$.

Example 158

3-{2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(6-methyl-2-pyridinyl)carbonyl]amino}pentanoyl)-amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 531 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.4-1.65(2H, m), 1.7-2.0(2H, m), 2.4-2.55(2H, m), 2.57(3H, s), 2.75-2.9(2H, m), 3.0-3.15(2H, m), 4.7-4.9(1H, m), 4.99(2H, m), 7.1-7.55(10H, m), 7.85-7.95(2H, m).

Example 159
Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(3,4-dimethylbenzoyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 582 $(M+Na)^+$.

Example 160
3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(3,4-dimethylbenzoyl)amino]pentanoyl}amino)-phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 544 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.45-1.7(2H, m), 1.75-1.95(2H, m), 2.27(6H, s), 2.4-2.5(2H, m), 2.75-2.9(2H, m), 2.95-3.15(2H, m), 4.5-4.7(1H, m), 5.00(2H, s), 7.05-7.45(10H, m), 7.6-7.8(2H, m).

Example 161
Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(3,4-dichlorobenzoyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 622, 624 $(M+Na)^+$.

Example 162

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(3,4-dichlorobenzoyl)amino]pentanoyl}amino)-phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 584, 586 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.45-1.7(2H, m), 1.75-1.95(2H, m), 1.4-1.55(2H, m), 2.75-2.9(2H, m), 3.0-3.15(2H, m), 4.5-4.7(1H, m), 5.01(2H, s), 7.1-7.4(9H, m), 7.76(1H, d, J=8.3Hz), 7.91(1H, dd, J=1.9, 8.4Hz), 8.20(1H, d, J=1.9Hz).

Example 163

Methyl 3-[2-({(2S)-5-({[(2-chlorobenzyl)oxy]-carbonyl}amino)-2-[(1H-indol-2-ylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((-)ESI) m/z : 603, 605 $(M-H)^-$.

Example 164

3-[2-({(2S)-5-({[(2-Chlorobenzyl)oxy]carbonyl}-amino)-2-[(1H-indol-2-ylcarbonyl)amino]pentanoyl}-amino)phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 589, 591 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.5-2.0(4H, m), 2.4-2.6(2H, m), 2.75-2.9(2H, m), 3.0-3.2(2H, m), 4.6-4.8(1H, m), 5.09(2H, s), 7.0-7.55(12H, m), 7.62(1H, d, J=7.8 Hz).

Example 165
Methyl 3-{2-[((2S)-5-({[(2-chlorobenzyl)oxy]-carbonyl}amino)-2-{[(1-methyl-1H-indol-2-yl)-carbonyl]amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 641, 643 $(M+Na)^+$.

Example 166
3-{2-[((2S)-5-({[(2-Chlorobenzyl)oxy]carbonyl}-amino)-2-{[(1-methyl-1H-indol-2-yl)carbonyl]-amino}pentanoyl)amino]phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 603,605 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.45-2.05(4H, m), 2.3-2.6(2H, m), 2.75-2.9(2H, m), 3.0-3.2(2H, m), 3.98(3H, s), 4.5-4.7(1H, m), 5.09(2H, s), 7.05-7.7(13H, m).

Example 167
Methyl 3-(2-{[(2S)-2-[(4-biphenylylcarbonyl)-amino]-5-({[(2-chlorobenzyl)oxy]carbonyl}amino)-

pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 664, 666 $(M+Na)^+$.

Example 168

3-(2-{[(2S)-2-[(4-Biphenylylcarbonyl)amino]-5-({[(2-chlorobenzyl)oxy]carbonyl}amino)pentanoyl]-amino}phenyl)propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 626, 628 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.5-2.0(4H, m), 2.4-2.6(2H, m), 2.75-2.9(2H, m), 3.05-3.2(2H, m), 4.55-4.75(1H, m), 5.09(2H, s), 7.1-7.6(11H, m), 7.7-7.85(4H, m), 8.03(2H, d, J=8.3Hz).

Example 169-1

Ethyl 2'-nitro-3-biphenylylcarboxylate

To a solution of 1-iodo-2-nitrobenzene (2.0g) and [3-(ethoxycarbonyl)phenyl]boronic acid (2.0g) in 1,2-dimethoxyethane (20mL), were added tetrakis(triphenyl)palladium(0) (0.93g) and 2M sodium carbonate (8.4mL) at room temperature. The mixture was stirred at 80℃ for 18 hours.

The resulting mixture was poured into water and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated under

reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 10 : 1 to 5 : 1) to give the target compound (1.2g).

MS ((+)ESI) m/z : 294 $(M+Na)^+$.

Example 169-2
Ethyl 2'-amino-3-biphenylylcarboxylate

To a solution of ethyl 2'-nitro-3-biphenylylcarboxylate (1.1g) obtained in Example 169-1 in a mixture of ethanol (15mL) and water (5mL), were added iron (679mg) and ammonium chloride (108mg) at room temperature under nitrogen. The mixture was refluxed for 1 hour.

The resulting mixture was filtered through celite, and the filtrate was evaporated under reduced pressure. The residue was dissolved into a mixture of saturated aqueous sodium bicarbonate and ethyl acetate. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, evaporated, and dried in vacuo to give the target compound (1.0g).

MS ((+)ESI) m/z : 242 $(M+H)^+$.

Example 169-3
Ethyl 2'-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-3-biphenylylcarboxylate

To a solution of (2S)-5-[[(benzyloxy)-carbonyl]amino]-2-[(tert-butoxycarbonyl)amino]-pentanoic acid (305mg) and ethyl 2'-amino-3-biphenylylcarboxylate (254mg) obtained in Example 169-2 in dichloromethane (7mL), were added

bromotripyrrolidinophosphonium hexafluorophosphate (490mg) and N,N-diisopropylethylamine (370 mg) at 5℃ under nitrogen. The mixture was stirred at room temperature for 12 hours.

The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 2 : 1 to 4 : 3) to give the target compound (357mg).

MS ((+)ESI) m/z : 612 $(M+Na)^+$.

Example 169-4

Ethyl 2'-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]-3-biphenylylcarboxylate hydrochloride

To a solution of ethyl 2'-[[(2S)-5-[[(benzyloxy)-carbonyl]amino]-2-[(tert-butoxycarbonyl)amino]-pentanoyl]amino]-3-biphenylylcarboxylate (292mg) obtained in Example 169-3 in ethyl acetate (2mL), was added hydrogen chloride (4N in ethyl acetate, 5mL) at room temperature under nitrogen. The mixture was stirred at the same temperature for 2 hours. The resulting mixture was evaporated dried in vacuo to give the target compound (281mg).

MS ((+)ESI) m/z : 490 $(M-HCl+H)^+$.

Example 169-5

Ethyl 2'-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-

amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]-3-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 656 $(M+Na)^+$.

Example 170

2'-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-3-biphenylylcarboxylic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 604 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.3-1.8(4H, m), 2.9-3.1(2H, m), 4.4-4.6(1H, m), 4.99(2H, s), 7.15-7.9(18H, m).

Example 171-1

Methyl 2'-nitro-4-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 169-1.

MS ((+)ESI) m/z : 280 $(M+Na)^+$.

Example 171-2

Methyl 2'-amino-4-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 169-2.

MS ((+)ESI) m/z : 228 $(M+H)^+$.

Example 171-3

Methyl 2'-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-4-biphenylylcarboxylate

To a solution of (2S)-5-[[(benzyloxy)-carbonyl]amino]-2-[(tert-butoxycarbonyl)amino]-pentanoic acid (300mg) and ethyl 2'-amino-4-biphenylylcarboxylate (232mg) in dichloromethane (10mL), were added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (342mg) and N,N-diisopropylethylamine (317mg) at 5 ℃ under nitrogen. The mixture was stirred at room temperature for 12 hours.

The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 2 : 1 to 1 : 1) to give the target compound (433mg).

MS ((+)ESI) m/z : 598 $(M+Na)^+$.

Example 171-4

Methyl 2'-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]-4-biphenylylcarboxylate hydrochloride

The target compound was obtained in a similar manner to that of Example 169-4.

MS ((+)ESI) m/z : 484 $(M-HCl+Na)^+$.

Example 171-5

Methyl 2'-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]-4-biphenylylcarboxylate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 642 $(M+Na)^+$.

Example 172

2'-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-4-biphenylylcarboxylic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 604 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.3-1.85(4H, m), 2.9-3.1(2H, m), 4.4-4.6(1H, m), 4.99(2H, s), 7.2-7.75(15H, m), 7.78 (1H, d, J=7.6Hz), 7.94(1H, d, J=8.1Hz).

Example 173-1

tert-Butyl [(2-aminophenyl)thio]acetate

To a suspension of sodium hydride (60% in oil, 703mg) in N, N-dimethylformamide (40mL), was added 2-aminobenzenethiol (2.0g) dropwise at 5℃ under nitrogen. The mixture was stirred at the same temperature for 40 minutes. To this one was added tert-butyl bromoacetate (3.4g), and the mixture was

stirred at 5℃ for 30 minutes.

The resulting mixture was poured into water and the aqueous was extracted with ethyl acetate. The organic layer was washed successively with water two times, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 10 : 1 to 5 : 1) to give the target compound (3.5g).

MS ((+)ESI) m/z : 262 $(M+Na)^+$.

Example 173-2

tert-Butyl {[2-({(2S)-5-{[(benzyloxy)carbonyl]-amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}-amino)phenyl]thio}acetate

The target compound was obtained in a similar manner to that of Example 171-3.

MS ((+)ESI) m/z : 610 $(M+Na)^+$.

Example 173-3

Methyl ({2-[((2S)-2-amino-5-{[(benzyloxy)-carbonyl]amino}pentanoyl)amino]phenyl}thio)acetate hydrochloride

To a solution of tert-butyl [[2-[[(2S)-5-[[(benzyloxy)carbonyl]amino]-2-[(tert-butoxy-carbonyl)amino]pentanoyl]amino]phenyl]thio}acetate (1.25g) obtained in Example 172-2 in dichloromethane (12.5mL), was added trifluoroacetic acid (2.5mL) at room temperature under nitrogen. The mixture was stirred at the same temperature for 24 hours.

The resulting mixture was evaporated and dried in vacuo. Thionyl chloride (380mg) was added to methanol (6.3mL) dropwise at 5℃ under nitrogen, and to this one was added a solution of the above obtained residue in methanol (3.5mL). The mixture was stirred at room temperature for 20 hours. The resulting mixture was evaporated under reduced pressure. The residue was washed with diisopropyl ether and dried in vacuo to give the target compound (997mg).

MS ((+)ESI) m/z : 446 $(M-HCl+H)^+$.

Example 173-4
Methyl ({2-[((2S)-5-{[(benzyloxy)carbonyl]-amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]-amino}pentanoyl)amino]phenyl}thio)acetate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 625 $(M+Na)^+$.

Example 174
({2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}pentanoyl)-amino]phenyl}thio)acetic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 587 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.45-2.1(4H, m), 3.0-3.2(2H, m), 3.65(2H, s), 3.99(3H, s), 4.55-4.75(H, m), 5.01(1H, s), 7.05-7.4(2H, m), 7.4-7.6(10H, m), 7.66(1H, d, J=7.8Hz), 7.76(1H, d, J=7.9Hz).

Example 175
Methyl {[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)-phenyl]thio}acetate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 623 $(M+Na)^+$.

Example 176
{[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(2-quinolinylcarbonyl)amino]pentanoyl}amino)phenyl]-thio}acetic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 585 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.4-1.7(2H, m), 1.85-2.2(2H, m), 3.0-3.2(2H, m), 3.67(2H, m), 4.75-4.95(1H, m), 4.99(2H, s), 7.15-7.95(11H, m), 8.1-8.25(3H, m), 8.61(1H, d, J=8.5Hz).

Example 177
Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(1H-indol-3-ylacetyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 573 $(M+Na)^+$.

Example 178
6-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(1H-indol-3-ylacetyl)amino]pentanoyl}amino)hexanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((+)ESI) m/z : 573 $(M+Na)^+$.
^{1}H-NMR (DMSO-d_6) : δ 1.1-1.8(12H, m), 2.17(2H, t, J=7.3Hz), 2.85-3.1(4H, m), 3.56(2H, d, J=3.2Hz), 4.1-4.3(1H, m), 5.00(2H, s), 6.85-7.1(2H, m), 7.15-7.45(8H, m).

Example 179
Methyl 6-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[3-(1H-indol-3-yl)propanoyl]amino}pentanoyl)-amino]hexanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 587 $(M+Na)^+$.

Example 180
6-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[3-(1H-indol-3-yl)propanoyl]amino}pentanoyl)amino]-hexanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 549 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.15-1.7(10H, m), 2.18(2H, t, J=7.2Hz), 2.35-2.6(2H, m), 2.8-3.1(6H, m), 4.1-4.3(1H,

m), 5.00(2H, s), 6.9-7.15(3H, m), 7.2-7.45(6H, m), 7.53(1H, d, J=7.5Hz).

Example 181

Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2,3-dihydro-1-benzofuran-2-ylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoate

A mixture of methyl (2E)-3-[2-[[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[[(benzyloxy)carbonyl]amino]pentanoyl]amino]-phenyl]acrylate (734mg) and 10% palladium on activated carbon (50% wet, 1.5g) in a mixture of methanol (20mL), N,N-dimethylformamide (10mL) and acetic acid (10mL) was stirred at 45℃ in the presence of hydrogen at an atmospheric pressure for 1.5 hours. Palladium on activated carbon was removed by filtration through celite and the filtrate was evaporated under reduced pressure.

To the mixture of the residue in a mixture of tetrahydrofuran (80mL) and water (20mL), was added benzyloxycarbonyl chloride (242mg) below 20℃ with adjusting pH to 8.5 with 1N sodium hydroxide. The mixture was stirred at room temperature for 2 hours. The resulting mixture was diluted with ethyl acetate and separated. The organic layer was washed successively with water three times and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 1 : 1 to 1 : 2) to give the target compound (214mg). Methyl 3-{2-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]phenyl}propanoate was also obtained.

MS ((+)ESI) m/z : 596 $(M+Na)^+$.

Example 182

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(2,3-dihydro-1-benzofuran-2-ylcarbonyl)amino]-pentanoyl}amino)phenyl]propanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 558 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.3-1.9(4H, m), 2.35-2.55(2H, m), 2.65-2.8(2H, m), 2.95-3.5(5H, m), 4.45-4.6(1H, m), 5.0-5.05(2H, m), 5.15-5.3(1H, m), 6.8-6.9(2H, m), 7.05-7.4(11H, m).

Example 183-1

3-(Tritylamino)-1-propanol

To a solution of 3-amino-1-propanol (3.0g) and triethylamine (4.45g) in dichloromethane (30mL), was added a solution of trityl chloride (11.7g) in dichloromethane (90mL) at 5℃ under nitrogen. The mixture was stirred at room temperature for 22 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 5 : 1 to 2 : 1) to give the target compound (1.36g).

MS ((+)ESI) m/z : 340 $(M+Na)^+$.

Example 183-2
3-(Tritylamino)propyl methanesulfonate

To a solution of 3-(tritylamino)-1-propanol (500mg) obtained in Example 183-1 in dichloromethane (10mL), were added triethylamine (0.40mL) and methanesulfonylchloride (0.165mL) at 5 ℃ under nitrogen. The mixture was stirred at the same temperature for 3 hours. The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, evaporated, and dried in vacuo to give the target compound (574mg).

MS ((+)ESI) m/z : 418 $(M+Na)^+$.

Example 183-3
Methyl {[3-(tritylamino)propyl]thio}acetate

To a solution of methyl mercaptoacetate (163mg) in N,N-dimethylformamide (13mL), was added sodium methoxide (159mg), followed by 3-(tritylamino)propyl methanesulfonate (553mg) obtained in Example 183-2 and tetrabutylammmonium iodide (568mg) at room temperature under nitrogen. The mixture was stirred at 50℃ for 30 minutes.

The resulting mixture was poured into water and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with water three times and brine, dried over anhydrous magnesium sulfate, evaporated, and dried in vacuo to give the target compound (466mg).

Example 183-4
Methyl [(3-aminopropyl)thio]acetate hydrochloride

To a solution of methyl [[3-(tritylamino)propyl]thio]acetate (463mg) obtained in Example 183-3 in dichloromethane (5mL), were added anisole (0.62mL) and trifluoroacetic acid (0.44mL) at 5℃ under nitrogen. The mixture was stirred at the same temperature for 2.5 hours. The resulting mixture was evaporated under reduced pressure. The residue was washed with isopropyl ether and dissolved into methanol, followed by addition of hydrogen chloride methanol reagent 10, evaporated, and drying in vacuo to give the target compound (234mg).

MS ((+)ESI) m/z : 164 $(M-HCl+H)^+$.

Example 183-5
Methyl (8S)-8-[(tert-butoxycarbonyl)amino]-3,9-dioxo-1-phenyl-2-oxa-14-thia-4,10-diazahexadecan-16-oate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 534 $(M+Na)^+$.

Example 183-6
Methyl (8S)-8-amino-3,9-dioxo-1-phenyl-2-oxa-14-thia-4,10-diazahexadecan-16-oate hydrochloride

The target compound was obtained in a similar manner to that of Example 169-4.

MS ((+)ESI) m/z : 434 $(M-HCl+Na)^+$.

Example 183-7
Methyl (8S)-8-[(1-benzofuran-2-ylcarbonyl)amino]-3,9-dioxo-1-phenyl-2-oxa-14-thia-4,10-diazahexadecan-16-oate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 578 $(M+Na)^+$.

Example 184
Sodium (8S)-8-[(1-benzofuran-2-ylcarbonyl)-amino]-3,9-dioxo-1-phenyl-2-oxa-14-thia-4,10-diazahexadecan-16-oate

To a solution of methyl (8S)-8-[(1-benzofuran-2-ylcarbonyl)amino]-3,9-dioxo-1-phenyl-2-oxa-14-thia-4,10-diazahexadecan-16-oate (63mg) in 1,4-dioxane (3mL), was added 1N sodium hydroxide (0.34mL) at room temperature. The mixture was stirred at 45℃ for 4.5 hours. The resulting mixture was poured into 1N hydrochloric acid, and the aqueous layer was extracted with a mixture of chloroform and methanol (5 : 1). The organic layer was dried over anhydrous magnesium sulfate, evaporated, and dried in vacuo to give the acid product. The residue was dissolved into methanol, added 1N sodium hydroxide (0.12mL), evaporated, and dried in vacuo to give the target compound (64mg).

MS ((+)ESI) m/z : 586 $(M+Na)^+$.
^{1}H-NMR (DMSO-d_6) : δ 1.35-1.9(6H, m), 2.45-2.6(2H, m), 2.91(2H, s), 2.95-3.25(4H, m), 4.35-4.5(1H, m),

4.99(2H, s), 7.25-7.85(10H, m).

Example 185-1
Ethyl 6-[(tert-butoxycarbonyl)amino]hexanoate

To a suspension of ethyl 6-aminohexanoate hydrochloride (1.5g) in tetrahydrofuran (20mL), were added triethylamine (853mg) and di-tert-butyl dicarbonate (1.84g) at 5℃ under nitrogen. The mixture was stirred at the same temperature for 40 minutes.

The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 5 : 1 to 3 : 1) to give the target compound (1.94g).

MS ((+)ESI) m/z : 282 $(M+Na)^+$.

Example 185-2
Ethyl 6-[(tert-butoxycarbonyl)(methyl)amino]-hexanoate

To a suspension of sodium hydride (60% in oil, 85mg) in N,N-dimethylformamide (6mL), was added a solution of ethyl 6-[(tert-butoxycarbonyl)amino]-hexanoate (500mg) obtained in Example 185-1 in N,N-dimethylformamide (2mL) at 5℃ under nitrogen. The mixture was stirred at the same temperature for 1 hour and at room temperature for 20 minutes. To this one was added iodomethane (301mg) at 5℃, and the

mixture was stirred at room temperature for 3 days.

The resulting mixture was poured into water, and the aqueous layer was extracted with a mixture of hexane and ethyl acetate (1 : 1). The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 10 : 1 to 5 : 1) to give the target compound (222mg).

MS ((+)ESI) m/z : 296 $(M+Na)^+$.

Example 185-3
Ethyl 6-(methylamino)hexanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 169-4.

MS ((+)ESI) m/z : 174 $(M-HCl+H)^+$.

Example 185-4
Ethyl 6-[{(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}(methyl)-amino]hexanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 544 $(M+Na)^+$.

Example 185-5
Ethyl 6-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)(methyl)amino]hexanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 169-4.

MS ((+)ESI) m/z : 422 $(M-HCl+H)^+$.

Example 185-6
Ethyl 6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-(methyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 588 $(M+Na)^+$.

Example 186
Sodium 6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-(methyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 536 $(M-Na)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.1-1.95(12H, m), 2.8-3.6(7H, m), 4.8-4.95(1H, m), 5.00(2H, s), 7.15-7.85(10H, m).

Example 187-1
9H-Fluoren-9-ylmethyl (4S)-4-(3-{[(benzyloxy)-carbonyl]amino}propyl)-5-oxo-1,3-oxazolidine-3-carboxylate

A mixture of (2S)-5-[[(benzyloxy)carbonyl]-amino]-2-[[(9H-fluoren-9-ylmethoxy)carbonyl]-amino]pentanoic acid (2.0g), paraformaldehyde

(1.23g) and p-toluenesulfonic acid hydrate (78mg) in toluene (40mL) was distilled for 40 minutes to remove water as toluene azeotrope.

The resulting mixture was poured into 5% aqueous sodium bicarbonate and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with 5% aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform / methanol = 20 : 1 to 10 : 1) to give a mixture (1.13g) of the target compound and (4S)-1-[(benzyloxy)carbonyl]-3-[(9H-fluoren-9-ylmethoxy)carbonyl]hexahydro-1H-1,3-diazepine-4-carboxylic acid.

MS ((+)ESI) m/z : 537 $(M+Na)^+$.

Example 187-2

(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[[(9H-fluoren-9-ylmethoxy)carbonyl](methyl)amino]-pentanoic acid

To a solution of a mixture (400mg) of 9H-fluoren-9-ylmethyl (4S)-4-[3-[[(benzyloxy)-carbonyl]amino]propyl]-5-oxo-1,3-oxazolidine-3-carboxylate and (4S)-1-[(benzyloxy)carbonyl]-3-[(9H-fluoren-9-ylmethoxy)carbonyl]hexahydro-1H-1,3-diazepine-4-carboxylic acid obtained in Example 187-1 in chloroform (6mL), were added trifluoroacetic acid (6mL) and triethylsilane (279mg) at room temperature under nitrogen. The mixture was stirred at the same temperature for 22 hours.

The resulting mixture was evaporated under reduced pressure. The residue was purified by column

chromatography on silica gel (chloroform / methanol = 50 : 1 to 5 : 1) to give the target compound (381mg).

MS ((+)ESI) m/z : 652 $(M+Na)^+$.

Example 187-3

Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[[(9H-fluoren-9-ylmethoxy)carbonyl](methyl)amino]-pentanoyl}amino)hexanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 652 $(M+Na)^+$.

Example 187-4

Methyl 6-{[(2S)-5-{[(benzyloxy)carbonyl]amino}-2-(methylamino)pentanoyl]amino}hexanoate

Piperidine (20% in N,N-dimethylformamide, 4mL) was added to methyl 6-[[(2S)-5-[[(benzyloxy)-carbonyl]amino]-2-[[(9H-fluoren-9-ylmethoxy)-carbonyl](methyl)amino]pentanoyl]amino]hexanoate (415mg) obtained in Example 187-3 at room temperature, and the mixture was stirred at the same temperature for 10 minutes. The resulting mixture was evaporated under reduced pressure. The residue was purified by reverse-phase column chromatography to give the target compound (129mg).

MS ((+)ESI) m/z : 408 $(M+H)^+$.

Example 187-5

Methyl 6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-(methyl)amino]-5-{[(benzyloxy)carbonyl]amino}-

pentanoyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 574 $(M+Na)^+$.

Example 188

Sodium 6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-(methyl)amino]-5-{[(benzyloxy)carbonyl]amino}-pentanoyl)amino]hexanoate

To a solution of methyl 6-[[(2S)-2-[(1-benzofuran-2-ylcarbonyl)(methyl)amino]-5-[[(benzyloxy)carbonyl]amino]pentanoyl]amino]-hexanoate (132mg) in 1,4-dioxane (10mL), was added 1N sodium hydroxide (0.36mL) at room temperature. The mixture was stirred at the same temperature for 16 hours.

The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform / methanol = 20 : 1 to 15 : 1), followed by treatment of 1N sodium hydroxide to give the target compound (57mg).

MS ((-)ESI) m/z : 536 $(M-Na)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.1-1.9(12H, m), 2.9-3.7(7H, m), 3.85-4.15(1H, m), 5.01(2H, s), 7.2-7.5(8H, m), 7.55-7.8(2H, m).

Example 189-1

Methyl (2S)-5-{[(benzyloxy)carbonyl]amino}-2-

(tritylamino)pentanoate

To a suspension of methyl (2S)-2-amino-5-[[(benzyloxy)carbonyl]amino]pentanoate hydrochloride (1.0g) and triethylamine (767mg) in dichloromethane (20mL), was added a solution of trityl chloride (968mg) in dichloromethane (4mL) at 5℃ under nitrogen. The mixture was stirred at room temperature for 12 hours.

The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with water three times, saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 3 : 1 to 2 : 1) to give the target compound (1.54g).

MS ((+)ESI) m/z : 545 $(M+Na)^+$.

Example 189-2

Methyl (2S)-5-[[(benzyloxy)carbonyl](methyl)-amino]-2-(tritylamino)pentanoate

To a suspension of sodium hydride (60% in oil, 42mg) in N,N-dimethylformamide (10mL), was added methyl (2S)-5-[[(benzyloxy)carbonyl]amino]-2-(tritylamino)pentanoate (500mg) obtained in Example 189-1 at 5℃ under nitrogen. The mixture was stirred at the same temperature for 50 minutes.

To this one was added iodomethane (149mg) at 5℃, and the mixture was stirred at room temperature for 4 hours. The resulting mixture was poured into water and the aqueous layer was extracted with ethyl acetate.

The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 5 : 1 to 3 : 1) to give the target compound (385mg).

MS ((+)ESI) m/z : 559 $(M+Na)^+$.

Example 189-3
Methyl (2S)-2-amino-5-[[(benzyloxy)carbonyl]-(methyl)amino]pentanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 183-4.

MS ((+)ESI) m/z : 295 $(M-HCl+H)^+$.

Example 189-4
Methyl (2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[[(benzyloxy)carbonyl](methyl)amino]pentanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 461 $(M+Na)^+$.

Example 189-5
(2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-[[(benzyloxy)carbonyl](methyl)amino]pentanoic acid

To a solution of methyl (2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[[(benzyloxy)-carbonyl](methyl)amino]pentanoate (267mg) obtained in Example 189-4 in methanol (5mL), was added 1N sodium

hydroxide (1.22mL) at room temperature. The mixture was stirred at the same temperature for 80 minutes. To this resulting mixture was added 1N hydrochloric acid (1.22mL), evaporated, and dried in vacuo to give the target compound (339mg).

MS ((-)ESI) m/z : 423 $(M-H)^-$.

Example 189-6

Methyl 6-({(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-[[(benzyloxy)carbonyl](methyl)amino]-pentanoyl}amino)hexanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 574 $(M+Na)^+$.

Example 190

Sodium 6-({(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-[[(benzyloxy)carbonyl](methyl)amino]-pentanoyl}amino)hexanoate

To a solution of methyl 6-[[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[[(benzyloxy)-carbonyl](methyl)amino]pentanoyl]amino]hexanoate (291mg) in methanol (5mL), was added 1N sodium hydroxide (0.61mL) at room temperature. The mixture was stirred at 45℃ for 130 minutes. The resulting mixture was evaporated and dried in vacuo to give the target compound (270mg).

MS ((+)ESI) m/z : 560 $(M+H)^+$.

^{1}H-NMR (DMSO-d_6) : δ 1.1-1.95(12H, m), 2.7-3.6(7H, m), 4.3-4.5(1H, m), 5.03(2H, s), 7.15-7.5(8H, m),

7.55-7.8(2H, m).

Example 191-1
Methyl 6-{[(4-nitrophenyl)sulfonyl]amino}hexanoate

To a suspension of methyl 6-aminohexanoate hydrochloride (500mg) in dichloromethane (15mL), were added 4-nitrobenzenesulfonyl chloride (640mg) and triethylamine (585mg) at 5℃ under nitrogen. The mixture was stirred at 5℃ for 1 hour.

The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with 1N hydrochloric acid, water and brine, dried over anhydrous magnesium sulfate, evaporated, and dried in vacuo to give the target compound (915mg).

MS ((+)ESI) m/z : 353 $(M+Na)^+$.

Example 191-2
Benzyl {(4S)-4-[(tert-butoxycarbonyl)amino]-5-hydroxypentyl}carbamate

To a solution of methyl 6-[[(4-nitrophenyl)sulfonyl]amino]hexanoate (3.0g) in tetrahydrofuran (30mL), were added N-methylmorpholine (828mg) and ethyl chloroformate (888mg) at -5℃ under nitrogen. The mixture was stirred at the same temperature for 20 minutes. To this one was added sodium borohydride (929mg) followed by methanol (30mL) dropwise at -5℃. The mixture was stirred at the same temperature for 2 hours.

1N Hydrochloric acid was added to the resulting mixture below 10℃ to adjust pH to 6.5. After concentration under reduced pressure, the residue was

poured into 1N hydrochloric acid, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with water, 5% aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 1 : 1 to 1 : 2) to give the target compound (2.45g).

MS ((+)ESI) m/z : 375 $(M+Na)^+$.

Example 191-3

Methyl 6-{{(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentyl}[(4-nitrophenyl)sulfonyl]amino}hexanoate

To a solution of methyl 6-[[(4-nitrophenyl)sulfonyl]amino]hexanoate (281mg) obtained in Example 191-1 and benzyl [(4S)-4-[(tert-butoxycarbonyl)amino]-5-hydroxypentyl]carbamate (450mg) obtained in Example 191-2 in dichloromethane (10mL), were added triphenylphosphine (402mg) and diethyl azodicarboxylate (0.241mL) at 5℃ under nitrogen. The mixture was stirred at room temperature for 5 hours.

The resulting mixture was poured into 1N hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 2 : 1 to 4 : 3) to give the target compound (200mg).

MS ((+)ESI) m/z : 687 $(M+Na)^+$.

Example 191-4
Methyl 6-{((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentyl)[(4-nitrophenyl)sulfonyl]amino}-hexanoate hydrochloride

The target compound was obtained in a similar manner to that of Example 169-4.

MS ((+)ESI) m/z : 565 $(M-HCl+H)^+$.

Example 191-5
Methyl 6-{((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentyl)-[(4-nitrophenyl)sulfonyl]amino}hexanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 731 $(M+Na)^+$.

Example 191-6
Methyl 6-[((2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentyl)(tert-butoxycarbonyl)amino]hexanoate

To a solution of methyl 6-[[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[[(benzyloxy)-carbonyl]amino]pentyl][(4-nitrophenyl)sulfonyl]-amino]hexanoate (129mg) obtained in Example 191-5 in N,N-dimethylformamide (2mL), were added potassium carbonate (76mg) and benzenethiol (0.037mL) at room temperature under nitrogen. The mixture was stirred at the same temperature for 15 hours.

To this one was added a solution of di-tert-butyl dicarbonate (99mg) in tetrahydrofuran (1mL) at room temperature, and the mixture was stirred at the same temperature for 2 hours. The resulting mixture was poured into 1N hydrochloric acid, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate, water two times and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 2 : 1 to 1 : 1) to give the target compound (71mg).

MS ((+)ESI) m/z : 623 $(M+Na)^+$.

Example 191-7
6-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentyl)(tert-butoxycarbonyl)amino]hexanoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 608 $(M-H)^-$.

Example 191-8
6-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentyl)amino]hexanoic acid hydrochloride

The target compound was obtained in a similar manner to that of Example 169-4.

MS ((-)ESI) m/z : 508 $(M-HCl-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.05-1.7(10H, m), 2.21(2H, t,

J=7.1 Hz), 2.8-3.2(6H, m), 4.15-4.4(1H, m), 4.99(2H, s), 7.15-7.9(10H, m).

Example 192-1

Methyl (2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(4-nitrophenyl)sulfonyl]amino}pentanoate

To a suspension of methyl (2S)-2-amino-5-[[(benzyloxy)carbonyl]amino]pentanoate hydrochloride (500mg) in dichloromethane (15mL), were added 4-nitrobenzenesulfonyl chloride (367mg) and triethylamine (335mg) at 5℃ under nitrogen. The mixture was stirred at room temperature for 12 hours. The resulting mixture was poured into 1N hydrochloric acid, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with 1N hydrochloric acid, water two times and brine, dried over anhydrous magnesium sulfate, evaporated, and dried in vacuo to give the target compound (760mg).

MS ((+)ESI) m/z : 488 $(M+Na)^+$.

Example 192-2

Methyl (2S)-5-{[(benzyloxy)carbonyl]amino}-2-{(4-biphenylylmethyl)[(4-nitrophenyl)sulfonyl]amino}-pentanoate

To a solution of methyl (2S)-5-[[(benzyloxy)carbonyl]amino]-2-[[(4-nitrophenyl)-sulfonyl]amino]pentanoate (744mg) obtained in Example 192-1 in N,N-dimethylformamide (10mL), were added potassium carbonate (331mg) and 4-(bromomethyl)biphenylyl (435mg) at room temperature under nitrogen. The mixture was stirred at the same temperature for 2.5 hours.

The resulting mixture was poured into water, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 2 : 1 to 4 : 3) to give the target compound (870mg).

MS ((+)ESI) m/z : 654 $(M+Na)^+$.

Example 192-3
(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{(4-biphenylylmethyl)[(4-nitrophenyl)sulfonyl]-amino}pentanoic acid

To a solution of methyl (2S)-5-[[(benzyloxy)carbonyl]amino]-2-[(4-biphenylyl-methyl)[(4-nitrophenyl)sulfonyl]amino]pentanoate (856mg) obtained in Example 192-2 in 1,4-dioxane (5mL), was added 1N sodium hydroxide (2.78mL) at room temperature. The mixture was stirred at the same temperature for 12 hours. The resulting mixture was poured into 1N hydrochloric acid, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, evaporated, and dried in vacuo to give the target compound (861mg).

MS ((-)ESI) m/z : 616 $(M-H)^-$.

Example 192-4
Methyl 6-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{(4-biphenylylmethyl)[(4-nitrophenyl)sulfonyl]-amino}pentanoyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 767 $(M+Na)^+$.

Example 192-5

Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(4-biphenylylmethyl)amino]pentanoyl}amino)-hexanoate

To a solution of methyl 6-[[(2S)-5-[[(benzyloxy)carbonyl]amino]-2-[(4-biphenylylmethyl)[(4-nitrophenyl)sulfonyl]amino]-pentanoyl]amino]hexanoate (415mg) obtained in Example 192-4 in N,N-dimethylformamide (5mL), were added potassium carbonate (231mg) and benzenethiol (123mg) at room temperature under nitrogen. The mixture was stirred at the same temperature for 12 hours.

The resulting mixture was poured into water, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform / methanol = 50 : 1 to 20 : 1) to give the target compound (206mg).

MS ((+)ESI) m/z : 560 $(M+H)^+$.

Example 193

Sodium 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(4-biphenylylmethyl)amino]pentanoyl}amino)-hexanoate

To a solution of methyl 6-[[(2S)-5-[[(benzyloxy)carbonyl]amino]-2-[(4-biphenylylmethyl)amino]pentanoyl]amino]hexanoate (202mg) in 1,4-dioxane (3mL), was added 1N sodium hydroxide (0.54mL) at room temperature. The mixture was stirred at 55℃ for 1.5 hours. To this resulting mixture was added 1N hydrochloric acid (0.18mL), evaporated, and dried in vacuo to give the target compound (210mg).

MS ((+)ESI) m/z : 568 $(M+H)^+$.
^{1}H-NMR (DMSO-d_6) : δ 1.15-1.6(10H, m), 1.84(2H, t, J=7.0Hz), 2.2-2.5(1H, m), 2.85-3.2(6H, m), 3.4-3.8(2H, m), 4.99(2H, s), 7.3-7.8(14H, m).

Example 194-1
Methyl 3-{2-[((2S)-5-{[(benzyloxy)carbonyl]-amino}-2-{[(4-nitrophenyl)sulfonyl]amino}-pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 192-1.

MS ((+)ESI) m/z : 635 $(M+Na)^+$.

Example 194-2
Methyl 3-{2-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{(4-biphenylylmethyl)[(4-nitrophenyl)sulfonyl]-amino}pentanoyl)amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 192-2.

MS ((+)ESI) m/z : 801 $(M+Na)^+$.

Example 194-3

Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(4-biphenylylmethyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 192-5.

MS ((+)ESI) m/z : 594 $(M+H)^+$.

Example 195

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(4-biphenylylmethyl)amino]pentanoyl}amino)phenyl]-propanoic acid

To a solution of methyl 3-[2-[[(2S)-5-[[(benzyloxy)carbonyl]amino]-2-[(4-biphenylyl-methyl)amino]pentanoyl]amino]phenyl]propanoate (90mg) in 1,4-dioxane (3mL), was added 1N sodium hydroxide (0.36mL) at room temperature. The mixture was stirred at 45℃ for 8.5 hours. To this resulting mixture was added 1N hydrochloric acid (0.36mL), and the mixture was stirred at room temperature for 3.5 hours. The precipitates were collected, washed with a mixture of 1,4-dioxane and water (3 : 1), and dried in vacuo to give the target compound (68mg).

MS ((-)ESI) m/z : 578 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.4-1.75(4H, m), 2.4-2.6(2H, m), 2.75-2.9(2H, m), 2.9-3.3(3H, m), 3.6-4.9(2H, m), 5.00(2H, s), 7.1-7.55(14H, m), 7.55-7.7(4H, m).

Example 196-1

Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[[(4-nitrophenyl)sulfonyl](2-quinolinylmethyl)-amino]pentanoyl}amino)phenyl]propanoate

To a solution of methyl 3-[2-[[(2S)-5-[[(benzyloxy)carbonyl]amino]-2-[[(4-nitrophenyl)-sulfonyl]amino]pentanoyl]amino]phenyl]propanoate (320mg) in N,N-dimethylformamide (7mL), were added potassium carbonate (173mg), potassium iodide (95mg) and 2-(chloromethyl)quinoline hydrochloride (123mg) at 5℃ under nitrogen. The mixture was stirred at room temperature for 24 hours.

The resulting mixture was poured into water, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed successively with water two times and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform / ethyl acetate = 3 : 1 to 2 : 1) to give the target compound (197mg).

MS ((+)ESI) m/z : 776 $(M+Na)^+$.

Example 196-2

Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-quinolinylmethyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 192-5.

MS ((+)ESI) m/z : 569 $(M+H)^+$.

Example 197

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(2-quinolinylmethyl)amino]pentanoyl}amino)-phenyl]propanoic acid

To a solution of methyl 3-[2-[[(2S)-5-[[(benzyloxy)carbonyl]amino]-2-[(2-quinolinylmethyl)amino]pentanoyl]amino]phenyl]propanoate (97mg) in 1,4-dioxane (3mL), was added 1N sodium hydroxide (0.43mL) at room temperature. The mixture was stirred at 45℃ for 6 hours. To this resulting mixture was added 1N hydrochloric acid (0.43mL), and the mixture was evaporated under reduced pressure. To the residue was added a mixture of chloroform and methanol (5 : 1), and the insoluble materials were removed by filtration. The filtrate was evaporated and dried in vacuo to give the target compound (97mg).

MS ((+)ESI) m/z : 555 $(M+H)^+$.

^{1}H-NMR (DMSO-d_6) : δ 1.45-1.8(4H, m), 2.45-2.6(2H, m), 2.75-2.9(2H, m), 2.95-3.3(3H, m), 3.9-4.2(2H, m), 5.00(2H, s), 7.1-7.8(12H, m), 7.9-8.0(2H, m), 8.25-8.35(1H, m).

Example 198

Methyl 4-[2-({(2S)-2,5-bis[(1-benzofuran-2-ylcarbonyl)amino]pentanoyl}amino)ethyl]benzoate

The target compound was obtained in a similar manner to that of Example 131.

MS ((+)ESI) m/z : 604 $(M+Na)^+$.

Example 199

4-[2-({(2S)-2,5-Bis[(1-benzofuran-2-ylcarbonyl)-amino]pentanoyl}amino)ethyl]benzoic acid

The target compound was obtained in a similar manner to that of Example 132.

MS ((-)ESI) m/z : 566 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.4-1.85(4H, m), 2.7-2.9(2H, m), 3.15-3.5(4H, m), 4.3-4.6(1H, m), 7.25-7.9(11H, m), 8.1-8.25(1H, m), 8.56(1H, d, J=8.1Hz), 8.65-8.8(1H, m).

Example 200-1
Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)-hexanoate

To a solution of (2S)-5-{[(benzyloxy)-carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]-pentanoic acid (15g) in N,N-dimethylformamide (150mL), were added successively 1-hydroxybenzotriazole (8.18g), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (8.3g). The mixture was stirred at room temperature for 2 hours. The mixture was quenched by the addition of water (300mL), and extracted with ethyl acetate (300mL). The extract was washed successively with water, saturated aqueous sodium hydrogencarbonate and brine (120 mL), and dried over magnesium sulfate. Filtration followed by evaporation gave the target compound (18.9g) as a white solid.

MS ((+)ESI) m/z : 516 $(M+Na)^+$.

Example 200-2
Methyl 6-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]-amino}pentanoyl)amino]hexanoate hydrochloride

To a suspension of methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]pentanoyl}amino)hexanoate

(15g) obtained in Example 200-1 in 1,4-dioxane (100mL), was added 4N hydrogen chloride in 1,4-dioxane (150mL). The mixture was stirred at room temperature for 3 hours. The solvent was removed by evaporation to give the target compound (13g) as a white solid.

MS ((+)ESI) m/z : 394 $(M-HCl+Na)^+$.

Example 200-3

Methyl 6-[((2S)-2-(benzoylamino)-5-{[(benzyloxy)-carbonyl]amino}pentanoyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 520 $(M+Na)^+$.

Example 201

6-[((2S)-2-(Benzoylamino)-5-{[(benzyloxy)-carbonyl]amino}pentanoyl)amino]hexanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 482 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.17-1.51(8H, m), 1.64-1.70(2H, m), 2.18(2H, t, J=7.2Hz), 4.32-4.43(1H, m), 4.99(2H, s), 7.23-7.35(6H, m), 7.41-7.54(3H, m), 7.86-7.96(3H, m), 8.36-8.40(1H, m).

Example 202

Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2,2-dimethylpropanoyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 500 $(M+Na)^+$.

Example 203

Sodium 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2,2-dimethylpropanoyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 41.

MS ((-)ESI) m/z : 462 $(M-Na)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.10(9H, s), 1.20-1.66(10H, m), 1.87-1.95(2H, m), 2.92-3.04(4H, m), 4.14-4.25(1H, m), 4.99(2H, s), 7.28-7.54(7H, m), 8.01-8.04(1H, m).

Example 204

Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-pyridinylcarbonyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 521 $(M+Na)^+$.

Example 205

Sodium 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(2-pyridinylcarbonyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 41.

MS ((-)ESI) m/z : 483 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.22-1.44(8H, m), 1.57-1.79(2H, m), 1.95-2.02(2H, m), 2.98-3.04(4H, m), 4.44-4.55(1H, m), 4.99(1H, s), 7.32-7.66(7H, m), 7.97-8.07(2H, m), 8.24-8.33(1H, m), 8.61-8.68(2H, m).

Example 206
Methyl 6-{[(2S)-5-{[(benzyloxy)carbonyl]amino}-2-(2-naphthoylamino)pentanoyl]amino}hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 570 $(M+Na)^+$.

Example 207
Sodium 6-{[(2S)-5-{[(benzyloxy)carbonyl]amino}-2-(2-naphthoylamino)pentanoyl]amino}hexanoate

The target compound was obtained in a similar manner to that of Example 41.

MS ((-)ESI) m/z : 596 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.23-1.47(10H, m), 1.85-1.92(2H, m), 3.01-3.07(4H, m), 4.42-4.53(1H, m), 4.99(2H, s), 7.27-7.63(8H, m), 7.94-8.06(4H, m), 8.42-8.47(1H, m), 8.65(1H, s), 9.12-9.16(1H, s).

Example 208
Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(4-biphenylylcarbonyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar

manner to that of Example 27-3.

MS ((+)ESI) m/z : 596 $(M+Na)^+$.

Example 209
6-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(4-biphenylylcarbonyl)amino]pentanoyl}amino)hexanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 558 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.20-1.56(8H, m), 1.71-1.73(2H, m), 2.18(2H, t, J=7.2Hz), 3.06(4H, m), 4.35-4.45(1H, m), 5.00(2H, s), 7.28-7.54(8H, m), 7.72-7.79(5H, m), 7.92-8.02(3H, m), 8.43-8.47(1H, m).

Example 210
Methyl 6-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(2E)-3-phenyl-2-propenoyl]amino}pentanoyl)-amino]hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 546 $(M+Na)^+$.

Example 211
Sodium 6-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(2E)-3-phenyl-2-propenoyl]amino}pentanoyl)-amino]hexanoate

The target compound was obtained in a similar manner to that of Example 41.

MS ((-)ESI) m/z : 509 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.22-1.65(10H, m), 1.84-1.91(2H, m), 2.97-3.04(4H, m), 4.30-4.37(1H, m), 4.99(2H, s), 6.92(1H, d, J=15.8Hz), 7.33-7.59(15H, m), 8.33-8.36(1H, m), 8.80-8.84(1H, m).

Example 212
Methyl 6-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(2E)-3-(3-pyridinyl)-2-propenoyl]amino}-pentanoyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 547 $(M+Na)^+$.

Example 213
Sodium 6-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(2E)-3-(3-pyridinyl)-2-propenoyl]amino}-pentanoyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 41.

MS ((-)ESI) m/z : 509 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.24-1.64(10H, m), 2.18(2H, t, J=7.2Hz), 2.98-3.11(4H, m), 4.30-4.41(1H, m), 5.00(2H, s), 6.91(1H, d, J=15.9Hz), 7.26-7.51(8H, m), 7.98-8.07(2H, m), 8.28-8.32(1H, m), 8.55-8.56(1H, m), 8.76-8.77(1H, m).

Example 214
Methyl 6-[((2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-

amino]hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 576 $(M+Na)^+$.

Example 215

6-[((2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-hexanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 538 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.17-1.72(10H, m), 2.18(2H, t, J=7.2Hz), 3.01-3.07(4H, m), 4.32-4.42(1H, m), 5.00(2H, s), 7.28-7.50(8H, m), 7.92-8.06(3H, m), 8.26(1H, s), 8.72-8.76(1H, m), 11.9(1H, s).

Example 216

Methyl 6-[((2S)-2-[(1H-benzimidazol-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 560 $(M+Na)^+$.

Example 217

6-[((2S)-2-[(1H-Benzimidazol-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-hexanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 522 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.17-1.53(8H, m), 1.74-1.77(2H, m), 2.19(2H, t, J=7.2Hz), 3.00-3.08(4H, m), 4.41-4.51(1H, m), 4.99(2H, s), 7.30-7.35(7H, m), 7.64-7.70(2H, m), 8.09-8.14(1H, m), 8.56-8.61(1H, m).

Example 218
Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(cyclopropylacetyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 498 $(M+Na)^+$.

Example 219
Sodium 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(cyclopropylacetyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 41.

MS ((-)ESI) m/z : 460 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 0.08-0.14(2H, m), 0.35-0.43(2H, m), 0.93(1H, m), 1.20-1.55(10H, m), 1.82-1.89(2H, m), 2.01-2.04(2H, m), 2.95-2.98(4H, m), 4.18-4.21(1H, m), 4.99(2H, s), 7.21-7.47(6H, m), 8.06-8.10(2H, m).

Example 220
Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(cyclopentylcarbonyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 512 $(M+Na)^+$.

Example 221
6-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(cyclopentylcarbonyl)amino]pentanoyl}amino)-hexanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 474 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.18-1.72(18H, m), 2.14-2.21(2H, m), 2.50-2.51(1H, m), 2.95-3.03(4H, m), 4.12-4.19(1H, m), 5.00(2H, s), 7.25-8.00(8H, m), 12.5(1H, br).

Example 222
Methyl 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(1H-pyrrol-2-ylcarbonyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 509 $(M+Na)^+$.

Example 223

Sodium 6-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(1H-pyrrol-2-ylcarbonyl)amino]pentanoyl}amino)-hexanoate

The target compound was obtained in a similar manner to that of Example 41.

MS ((-)ESI) m/z : 471 $(M-Na)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.13-1.75(10H, m), 1.98-2.05(2H, m), 2.97-3.06(4H, m), 4.31-4.38(1H, m), 4.99(2H, s), 6.06(1H, m), 6.83-6.84(2H, m), 7.33-7.47(6H, m), 8.10(1H, m), 8.44-8.49(1H, m).

Example 224
Methyl 6-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}-pentanoyl)amino]hexanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 573 $(M+Na)^+$.

Example 225
6-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}-pentanoyl)amino]hexanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 535 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.26-1.49(8H, m), 1.72(2H, m), 2.15-2.22(2H, m), 3.02-3.05(4H, m), 3.96(3H, s), 4.36-4.38(1H, m), 5.00(2H, s), 6.93-7.74(10H, m),

7.95-8.01(2H, m), 8.38-8.42(1H, m), 12.6(1H, br).

Example 226

Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(1H-indol-2-ylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 593 $(M+Na)^+$.

Example 227

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(1H-indol-2-ylcarbonyl)amino]pentanoyl}amino)phenyl]-propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 555 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.59-1.62(2H, m), 1.81-1.91(2H, m), 2.46-2.53(2H, m), 2.79-2.86(2H, m), 3.07-3.10(2H, m), 4.63-4.74(1H, m), 5.00(2H, s), 7.07-7.64(14H, m), 8.57-8.61(1H, m), 9.58(1H, br-s), 11.6(1H, br-s), 12.1(1H, br-s).

Example 228

Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(4-biphenylylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 630 $(M+Na)^+$.

Example 229

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(4-biphenylylcarbonyl)amino]pentanoyl}amino)phenyl]-propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 592 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.58-1.61(2H. m), 1.88(2H, m), 2.45-2.51(2H, m), 2.78-2.85(2H, m), 3.06-3.09(2H, m), 4.59-4.69(1H, m), 5.01(2H, s), 7.15-7.53(13H, m), 7.72-7.80(4H, m), 8.03(2H, d, J=8.3Hz), 8.64-8.68(1H, m), 9.55(1H, s), 12.1(1H, br-s).

Example 230

Methyl 3-[2-({(2S)-5-{[(benzyloxy)carbonyl]amino}-2-[(6-quinolinylcarbonyl)amino]pentanoyl}amino)-phenyl]propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 605 $(M+Na)^+$.

Example 231

3-[2-({(2S)-5-{[(Benzyloxy)carbonyl]amino}-2-[(6-quinolinylcarbonyl)amino]pentanoyl}amino)phenyl]-propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 567 $(M-H)^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.51-1.64(2H, m), 1.81-1.92(2H, m), 2.48-2.52(2H, m), 2.79-2.86(2H, m), 3.08-3.11(2H, m), 4.64-4.76(1H, m), 5.00(2H, s), 7.13-7.35(10H, m), 7.79-7.86(1H, m), 8.19-8.35(2H, m), 8.73-8.80(2H, m), 8.96-8.99(1H, m), 9.13-9.16(1H, m), 9.63(1H, s).

Example 232
3-{2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(2-naphthyloxy)carbonyl]amino}pentanoyl)amino]-phenyl}propanoic acid

To a solution of methyl 3-{2-[((2S)-2-amino-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoate hydrochloride (100mg) in tetrahydofuran (1mL), was added 1N sodium hydoxide (0.65mL). The solution was stirred at room temperature for 1 hour. To the solution was added 2-naphthyl chloridocarbonate (49mg) at 4℃. The mixture was stirred at room temperature over night.

To the mixture was added water and the mixture was extracted with ethyl acetate. The extract was washed with brine, filtrated, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel with chloroform and methanol to give the target compound as a white solid.

MS ((+)ESI) m/z : 606 $(M+Na)^+$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.64-1.84(6H, m), 2.77-2.84(2H, m), 3.07-3.09(2H, m), 4.28(1H, m), 5.02(1H, s), 7.17-7.36(11H, m), 7.47-7.65(3H, m), 7.88-7.95(3H, m), 8.17-8.21(1H, m), 9.59(1H, br-s), 12.1 (1H, br-s).

Example 233-1
Methyl (2S)-2-[(1-benzothien-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 463 $(M+Na)^+$.

Example 233-2
(2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 425 $(M-H)^-$.

Example 233-3
Methyl 4-{2-[((2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]ethyl}benzoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 610 $(M+Na)^+$.

Example 234
4-{2-[((2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-ethyl}benzoic acid

The target compound was obtained in a similar

manner to that of Example 28.

MS ((-)ESI) m/z : 572(M-H)$^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.34-1.79(4H, m), 2.80(2H, t, J=6.8Hz), 3.01(2H, dd, J=6.3, 12.0Hz), 4.31-4.42(1H, m), 7.27-7.35(8H, m), 7.40-7.50(2H, m), 7.85(2H, d, J=8.0Hz), 7.93-8.05(3H, m), 8.12(1H, t, J=5.5Hz), 8.25(1H, s), 8.74(1H, d, J=8.0Hz), 12.80(1H, br-s).

Example 235
Methyl (2E)-3-{2-[((2S)-2-[(1-benzothien-2-yl-carbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}-pentanoyl)amino]phenyl}acrylate

The target compound was obtained in a similar manner to that of Example 27-1.

MS ((+)ESI) m/z : 608 (M+Na)$^+$.

Example 236
(2E)-3-{2-[((2S)-2-[(1-Benzothien-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]phenyl}acrylic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 570(M-H)$^-$.
^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.51-1.72(2H, m), 1.79-2.00(2H, m), 3.03-3.14(2H, m), 4.63-4.74(1H, m), 5.01(2H, s), 6.48(1H, d, J=15.6Hz), 7.21-7.49(11H, m), 7.73-7.83(2H, m), 7.94-8.05(2H, m), 8.30(1H, s), 8.94(1H, d, J=7.5Hz), 10.03(1H, s), 12.39(1H, br-s).

Example 237

Methyl 3-{2-[((2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]phenyl}propanoate

The target compound was obtained in a similar manner to that of Example 34-1.

MS ((+)ESI) m/z : 610 $(M+Na)^+$.

Example 238

3-{2-[((2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-phenyl}propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((+)ESI) m/z : 596 $(M+Na)^+$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.51-1.71(2H, m), 1.78-1.98(2H, m), 2.44-2.52(2H, m), 2.82(2H, t, J=7.0Hz), 3.03-3.14(2H, m), 4.58-4.70(1H, m), 5.01(2H, s), 7.10-7.36(10H, m), 7.40-7.51(2H, m), 7.94-8.05(2H, m), 8.29(1H, s), 8.93(1H, d, J=8.0Hz), 9.61(1H, s), 12.15(1H, br-s).

Example 239

Methyl 3-(2-{[(2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-({[(2-chlorobenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoate

The target compound was obtained in a similar manner to that of Example 27-3.

MS ((+)ESI) m/z : 644 $(M+Na)^+$.

Example 240

3-(2-{[(2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-({[(2-chlorobenzyl)oxy]carbonyl}amino)-pentanoyl]amino}phenyl)propanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((-)ESI) m/z : 606 $(M-H)^-$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 1.50-1.71(2H, m), 1.80-1.99(2H, m), 2.43-2.54(2H, m), 2.82(2H, t, J=7.5Hz), 3.05-3.14(2H, m), 4.59-4.69(1H, m), 7.12-7.50(10H, m), 7.94-8.05(2H, m), 8.29(1H, s), 8.93(1H, d, J=7.5Hz), 9.59(1H, s), 12.21(1H, br-s),

Example 241

Ethyl 4-{2-[((2S)-2-[(1-benzothien-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]phenyl}butanoate

The target compound was obtained in a similar manner to that of Example 27-1.

MS ((+)ESI) m/z : 638 $(M+Na)^+$.

Example 242

4-{2-[((2S)-2-[(1-Benzothien-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-phenyl}butanoic acid

The target compound was obtained in a similar manner to that of Example 28.

MS ((+)ESI) m/z : 610 $(M+Na)^+$.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 0.54-1.95(6H, m), 2.22(2H,

t, J=7.5Hz), 2.57(2H, t, J=8.0Hz), 3.04-3.14(2H, m), 4.59-4.70(1H, m), 5.01(2H, s), 7.13-7.51(10H, m), 7.94-8.05(2H, m), 8.30(1H, s), 8.93(1H, d, J=7.5Hz), 9.50(1H, s), 12.05(1H, br-s).

Example 243-1
(2S)-2-(1-Benzofuran-2-ylcarbonyl)amino-5-[(benzyloxycarbonyl)amino]pentanoic acid

To a solution of (2S)-2-amino-5-[(benzyloxycarbonyl)amino]pentanoic acid (5.0g, 18.77mmol) in NMP (50mL), was added BSA (11.6mL, 46.93mmol), and the mixture was stirred for 1 hour at room temperature. To the reaction mixture was added a mixture of 1-benzofuran-2-carboxylic acid (3.35g, 20.65mmol), PyBOP (10.74g, 20.65mmol) and DIEA (7.37mL, 41.29mmol) in NMP (40mL). The mixture was stirred 24 hours at room temperature.

The resultant mixture was partitioned between 25% n-hexane in EtOAc and 10% aqueous $KHSO_4$ solution. The organic phase was separated, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica-gel ($CHCl_3$-MeOH 9:1) to give the target compound (4.1g, 49.9%) as a foam.

MS ((-)ESI) m/z : 409 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.40-1.95(4H, m), 2.95-3.10(2H, m), 4.30-4.45(1H, m), 5.01(2H, s), 7.25-7.45(7H, m), 7.44-7.53(1H, m), 7.63-7.82(3H, m), 8.85(1H, d, J=7.9Hz).

Example 243-2
(2E)-3-{2-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-

amino]phenyl}acrylic acid

In the 60 mL polypropylene tube with polyethylene flits, to a suspension of wang resin (2.5g, 0.81mmole/g), 2-nitrocinnamic acid (782.3mg, 4.05mmol), triphenylphpsphine (1.18g, 4.05mmol) in THF (20mL), was added DEAD (637.8μL, 4.05mmol). The mixture was shaken for 4 hours at room temperature. After drained the solvent, the resin was washed well with THF and the carboxylic acid loading reaction was repeated. The solvent was drained, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure.

To the above resin was added DCM (20mL), pyridine (6.55mL, 1.62mmol) and Ac_2O (3.83mL, 40.5mmol). The mixture was shaken overnight at room temperature. After drained the solvent, the resin was washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure. The resulted resin was treated with 2M $SnCl_2$-H_2O in DMF (20mL×2) for 2 hours for the reduction of nitro group. Then, the resin was filtered, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure to give 2-aminocinnamic acid loaded wang resin. The obtained resin was divided 2 reaction vessels (2.02mmol each).

To a suspension of the above 2-aminocinnamic acid loaded wang resin (2.02mmol), (2S)-2-(1-benzofuran-2-ylcarbonyl)amino-5-[(benzyloxycarbonyl)amino]-pentanoic acid (3.03mmol) obtained in Example 243-1 and PyBroP (1.42g, 3.03mmol) in NMP (15mL), was added DIEA (1.08mL, 6.06mmol). The mixture was shaken for 3 days at room temperature. The solvent was drained, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure. After treated with 50% TFA in DCM (20mL) for 1 hour, the resin was filtered

and washed with DCM (15mL×2). The filtrates were combined, evaporated and purified by HPLC (reverse phase C_{18}, 5μ, 30mm×50mm column, 254nm, gradient 10-90% 0.05% TFA in CH_3CN / 0.05% TFA in H_2O, 40mL/min.). The fractions containing the target compound were combined, evaporated, and dried under reduced pressure to give the target compound.

MS ((-)ESI) m/z : 554 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.45-2.05(4H, m), 3.00-3.15(2H, m), 4.60-4.80(1H, m), 5.00(2H, s), 6.48(1H, d, J=15.8Hz), 7.20-7.55(12H, m), 7.69(2H, d, J=9.4Hz), 7.75-7.85 (2H, m), 8.76(1H, d, J=7.7Hz), 10.03(1H, S), 12.41(1H, br-s).

Example 244-1

(2S)-5-(Benzyloxycarbony)amino-2-{[(4-biphenylyl-amino)carbonyl]amino}pentanoic acid

To a solution of (2S)-2-amino-5-[(benzyloxycarbonyl)amino]pentanoic acid (5.0g, 18.77mmol) in THF (50mL), was added BSA (11.6mL, 46.93mmol). The mixture was stirred for 1 hour at room temperature. To the reaction mixture was added 4-biphenylyl isocyanate (4.03g, 20.65mmol) and the mixture was stirred 24 hours at room temperature. The resultant mixture was partitioned between EtOAc and 10% aqueous $KHSO_4$ solution. The organic phase was separated, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica-gel ($CHCl_3$ - MeOH = 9:1) to give the target compound (6.74g, 73.4%) as a foam.

MS ((-)ESI) m/z : 460 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.40-1.85(4H, m), 2.95-3.10(2H, m), 4.10-4.25(1H, m), 5.01(2H, s), 6.51(1H, d, J=7.9Hz), 7.25-7.65(15H, m), 8.75(1H, s), 12.76(1H, br-s).

Example 244-2
(2E)-3-{2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(4-biphenylylamino)carbonyl]amino}pentanoyl)-amino]phenyl}acrylic acid

The target compound was obtained from (2S)-5-(benzyloxycarbony)amino-2-{[(4-biphenylyl-amino)carbonyl]amino}pentanoic acid obtained in Example 244-1 in a similar manner to that of Example 243-2.

MS ((-)ESI) m/z : 605 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.50-1.90(4H, m), 3.00-3.15(2H, m), 4.50-4.65(1H, m), 5.00(2H, s), 6.48(1H, d, J=15.8Hz), 6.56(1H, d, J=8.2Hz), 7.25-7.80(20H, m), 8.81(1H, s), 10.06(1H, S), 12.43(1H, s).

Example 245
{3-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-phenyl}acetic acid

The target compound was obtained in a similar manner to that of Example 243-1 and 243-2.

MS ((-)ESI) m/z : 542 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.40-1.95(4H, m), 2.95-3.15(2H, m), 3.50-3.65(2H, m), 4.50-4.65(1H, m), 5.00(2H, s), 6.96(1H, d, J=7.6Hz), 7.20-7.55(11H, m), 7.65-7.85(3H, m), 8.75(1H, d, J=7.7Hz), 10.15(1H, S).

Example 246
{3-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(4-biphenylylamino)carbonyl]amino}pentanoyl)amino]-phenyl}acetic acid

The target compound was obtained in a similar manner to that of Example 243-1 and 243-2.

MS ((-)ESI) m/z : 593 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.40-1.80(4H, m), 2.95-3.15(2H, m), 3.55-3.65(2H, m), 4.35-4.50(1H, m), 5.00(2H, s), 6.54(1H, d, J=8.2Hz), 6.96(1H, d, J=7.5Hz), 7.20-7.70(17H, m), 8.80(1H, s), 10.16(1H, S).

Example 247
(2E)-3-{3-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)-amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)-amino]phenyl}acrylic acid

The target compound was obtained in a similar manner to that of Example 243-1 and 243-2.

MS ((-)ESI) m/z : 554 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.40-2.05(4H, m), 3.00-3.15(2H, m), 4.50-4.70(1H, m), 5.00(2H, s), 6.43(1H, d, J=15.9Hz), 7.25-7.90(16H, m), 7.69(2H, d, J=9.4Hz), 8.80(1H, d, J=7.7Hz), 10.26(1H, S).

Example 248
(2E)-3-{3-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(4-biphenylylamino)carbonyl]amino}-pentanoyl)-amino]phenyl}acrylic acid

The target compound was obtained in a similar manner to that of Example 243-1 and 243-2.

MS ((-)ESI) m/z : 605 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.40-1.90(4H, m), 2.95-3.15(2H, m), 4.35-4.50(1H, m), 5.00(2H, s), 6.43(1H, d, J=15.9Hz), 6.57(1H, d, J= 8.2Hz), 7.25-7.70(19H, m), 7.88(1H, s), 8.80(1H, s), 10.28(1H, S), 12.45(1H, br-s).

Example 249-1
6-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-amino}-pentanoyl)amino]hexanoic acid loaded wang resin

In the 60 mL polypropylene tube with polyethylene flits, a suspension of wang resin (3.5g, 0.81mmole/g), 6-(9-fluorenylmethoxycarbonylamino)hexanoic acid (3.7g, 11.4mmol), MSNT (3.38g, 11.4mmol) and NMI (3.62mL, 45.4mmol) in DCM (25mL) was shaken for 2 days at room temperature. The solvent was drained, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure. To the above resin was added DCM (25mL), pyridine (9.19mL, 113.6mmol) and Ac_2O (5.37mL, 56.8mmol). The mixture was shaken overnight at room temperature. After drained the solvent, the resin was washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure.

The resulted resin was treated with 20% piperidine in DMF (25mL×2) for 1 hour to remove Fmoc group. Then, the solvent was drained, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure to give 6-aminohexanoic acid loaded wang resin (Theoretical loading, 0.74 mmol/g).

To a suspension of the above 6-aminohexanoic acid loaded wang resin (2.55g, 1.89mmol) and (2S)-5-(benzyloxycarbony)amino-2-(9-fluorenyl-methoxycarbonylamino)pentanoic acid (2.77g,

5.67mmol) in NMP (25mL), was added HATU (2.15g, 5.67mmol) and DIEA (2.02mL, 11.34mmol). The mixture was shaken for 24 hours at room temperature. The solvent was drained, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure. The resulted resin was treated with 20% piperidine in DMF (25mL×2) for 1 hour to remove Fmoc group. Then, the solvent was drained, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure to the target compound.

Example 249-2

6-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(2-naphthyloxy)carbonyl]amino}pentanoyl)amino]-hexanoic acid

To a suspension of 6-[((2S)-5-{[(benzyloxy)-carbonyl]amino}-2-amino} pentanoyl)amino]hexanoic acid loaded wang resin (1.89mmol) obtained in Example 249-1 and pyridine (917.2 μL, 11.34mmol) in DCM (25mL), was added 2-naphthyl chloroformate (1.17g, 5.67mmol). The mixture was shaken for 2 days at room temperature.

The solvent was drained, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure. After treated with 50% TFA in DCM (20mL) for 1 hour, the resin was filtered and washed with DCM (15mL×2). The filtrates were combined, evaporated and purified by HPLC (reverse phase C_{18}, 5 μ, 30mm ×50mm column, 254nm, gradient 10-90% 0.05% TFA in CH_3CN / 0.05% TFA in H_2O, 40mL/min.). The fractions containing the target compound were combined, evaporated, and dried under reduced pressure to give the target compound.

MS ((+)ESI) m/z : 572 $(M+Na)^+$.
^{1}H-NMR (DMSO-d_6) : δ 1.20-1.70(10H, m), 2.19(2H, t, J=7.3Hz), 2.95-3.15(4H, m), 3.90-4.05(1H, m), 5.02(2H, s), 7.25-7.65(10H, m), 7.85-8.05(5H, m), 12.02(1H, s).

Example 250

6-({(2*S*)-5-{[(Benzyloxy)carbonyl]amino}-2-[(4-biphenylylsulfonyl)amino]pentanoyl}amino)hexanoic acid

To a suspension of 6-[((2S)-5-{[(benzyloxy)carbonyl]amino}-2-amino} pentanoyl)amino]hexanoic acid loaded wang resin (1.89mmol) obtained in Example 249-1 and pyridine (917.2 μL, 11.34mmol) in DCM (25mL), was added 4-biphenylsulfonyl chloride (1.43g, 5.67mmol). The mixture was shaken for 2 days at room temperature.

The solvent was drained, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure. After treated with 50% TFA in DCM (20mL) for 1 hour, the resin was filterd and washed with DCM (15mL×2). The filtrates were combined, evaporated, and purified by HPLC (reverse phase C_{18}, 5μ, 30mm×50mm column, 254nm, gradient 10-90% 0.05% TFA in CH_3CN / 0.05% TFA in H_2O, 40mL/min.). The fractions containing the target compound were combined, evaporated and dried under reduced pressure to give the target compound.

MS ((-)ESI) m/z : 594 $(M-H)^-$.
^{1}H-NMR (DMSO-d_6) : δ 1.10-1.50(10H, m), 2.09(2H, t, J=7.3Hz), 2.70-2.85(2H, m), 2.85-3.00(2H, m), 3.55-3.75(1H, m), 4.98(2H, s), 7.20-7.55(9H, m), 7.65-8.00(8H, m), 11.99(1H, br-s).

Example 251

6-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(4'-hydroxy-4-biphenylyl)carbonyl]amino}pentanoyl)-amino]hexanoic acid

To a suspension of 6-[((2S)-5-{[(benzyloxy)-carbonyl]amino}-2-amino} pentanoyl)amino]hexanoic acid loaded wang resin (1.89mmol) obtained in Example 249-1, 4-(4-hydroxyphenyl)benzoic acid (1.21g, 5.67mmol) and HATU (2.15g, 5.67mmol) in NMP (20mL), was added DIEA (2.02mL, 11.34mmol). The mixture was shaken for 2 days at room temperature.

The solvent was drained, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure. After treated with 50% TFA in DCM (20mL) for 1 hour, the resin was filterd and washed with DCM (15mL×2). The filtrates were combined, evaporated and purified by HPLC (reverse phase C_{18}, 5μ, 30mm×50mm column, 254nm, gradient 10-90% 0.05% TFA in CH_3CN / 0.05% TFA in H_2O, 40mL/min.). The fractions containing the target compound were combined, evaporated, and dried under reduced pressure to give the target compound.

MS ((-)ESI) m/z : 574 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.20-1.80(10H, m), 2.18(2H, t, J=7.3Hz), 2.95-3.15(4H, m), 4.30-4.45(1H, m), 5.00(2H, s), 6.87(2H, d, J=8.6Hz), 7.20-7.35(6H, m), 7.57(2H, d, J=8.6Hz), 7.67(2H, d, J=8.3Hz), 7.94(2H, d, J=8.3Hz), 8.37(1H, d, J=8.0Hz), 9.66(1H, s), 12.00(1H, br-s).

Example 252-1

3-{2-[((2S)-2-Amino]-5-{[(4-methylphenyl)diphenyl-methyl]amino}pentanoyl)amino]phenyl}propanoic acid loaded resin

To a suspension of 4-(4-formyl-3-methoxyphenoxy)-butylyl AM resin (18g, 0.51mmole/g) in a mixture of THF (200mL) and MeOH (5mL), was added $NaBH_4$ (695mg, 18.37mmol). The mixture was shaken for 24 hours at room temperature. The resin was collected by filtration, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure.

To the suspension of the above resin, 2-nitrocynnamic acid (2.66g, 13.77mmol) and triphenylphpsphine (3.61g, 13.77mmol) in THF (200mL), was added DEAD (2.17mL, 13.77mmol). The mixture was shaken for 24 hours at room temperature. After drained the solvent, the resin was washed well with THF, and the carboxylic acid loading reaction was repeated. The resin was collected by filtration, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure.

After treatment with a mixture of Ac_2O (17.36mL, 18.36mmol) and pyridine (29.7mL, 36.72mmol) in DCM (200mL) for 24 hours at room temperature, to the resulted resin was added 2M $SnCl_2$-H_2O in DMF (150mL ×2) for 2 hours. Then, the resin was collected by filtration, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure to give 2-aminocinnamic acid loaded resin.

To a suspension of the above 2-aminocinnamic acid loaded resin (9.18mmol) and (2S)-2-(9-fluorenylmethoxycarbonyl)amino-5-{[(4-methylphenyl)diphenylmethyl]amino}pentanoic acid (16.8g, 27.54mmol) and PyBroP (12.84g, 27.54mmol) in DMF (200mL), was added DIEA (9.83mL, 55.08mmol). The mixture was shaken for 2 days at room temperature. The resin was collected by filtration, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under

reduced pressure. After the removal of Fmoc group with 20% piperidine in DMF (150mL×2) for 1 hour, the resin was collected by filtration, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure to give the target compound.

Example 252-2
3-{2-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-phenyl}propanoic acid

To a suspension of 3-{2-[((2S)-2-amino]-5-{[(4-methylphenyl)diphenylmethyl]amino}pentanoyl)-amino]phenyl}propanoic acid loaded resin (4.59mmol) obtained in Example 252-1, 1-benzofuran-2-carboxylic acid (2.24g, 13.77mmol) and HATU (5.24g, 13.77mmol) in NMP (100mL), was added DIEA (4.92mL, 27.54mmol). The mixture was shaken for 4 days at room temperature. The resin was collected by filtration, washed well subsequently with DMF, MeOH, DCM, Et_2O, and dried under reduced pressure. After treated with 5% TFA in DCM (100mL) for 1 hour, the resin was filterd and washed with DCM (50mL×2). The filtrates were combined, evaporated and purified by HPLC (reverse phase C_{18}, 5μ, 30mm×50mm column, 254nm, gradient 10-90% 0.1% TFA in CH_3CN / 0.1% TFA in H_2O, 40mL/min.). The fractions containing the target compound were combined, evaporated, and dried under reduced pressure to give 3-{2-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-aminopentanoyl)amino] phenyl}propanoic acid (200mg).

A mixture of the above 3-{2-[((2S)-2-[(1-Benzofuran-2-ylcarbonyl)amino]-5-aminopentanoyl)amino] phenyl}propanoic acid (190mg, 0.45mmol) and 10% palladium on carbon (50% wet, 20mg)

in MeOH (5mL) was hydrogenated at atmospheric pressure of hydrogen at room temperature. After 4 hours, the catalyst was removed by filtration and evaporated to give residue, which was dissolved in DCM (30mL). To the resulting mixture was added 1-(benzyloxycarbonyloxy)benzotriazole-6-carboxamidomethyl polystyrene (2.42g, 0.93mmole/g) and shaken for 1 week at room temperature. The resin was removed by filtration and evaporation of the solvent gave a residue, which was purified by HPLC (reverse phase C_{18}, 5μ, 30mm×50mm column, 254nm, gradient 10-90% 0.1% TFA in CH_3CN / 0.1% TFA in H_2O, 40mL/min.). The fractions containing the target compound were combined, evaporated, and dried under reduced pressure to give the target compound (63.2mg).

MS ((-)ESI) m/z : 556 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.45-2.05(4H, m), 2.40-2.55(2H, m), 2.81(2H, t, J=7.5Hz), 3.00-3.15(2H, m), 4.60-4.75(1H, m), 5.00(2H, s), 7.15-7.55(12H, m), 7.65-7.85(3H, m), 8.75(1H, d, J=7.7Hz), 9.60(1H, S), 12.15(1H, br-s).

Example 253

3-{2-[((2S)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(4-biphenylylamino)carbonyl]amino}pentanoyl)amino]-phenyl}propanoic acid

A suspension of 3-{2-[((2S)-2-amino]-5-{[(4-methylphenyl)diphenylmethyl]amino}pentanoyl)-amino]phenyl}propanoic acid loaded resin (4.59mmol) obtained in Example 252-1 and 4-biphenylyl isocyanate (2.69g, 13.77mmol) in DCM (100mL) was shaken for 4 days at room temperature. The resin was collected by filtration, washed well subsequently with DMF, MeOH,

DCM, Et_2O, and dried under reduced pressure. After treated with 5% TFA in DCM (100mL) for 1 hour, the resin was filtered, and washed with DCM (50mL×2). The filtrates were combined, evaporated, and purified by HPLC (reverse phase C_{18}, 5μ, 30mm×50mm column, 254nm, gradient 10-90% 0.1% TFA in CH_3CN / 0.1% TFA in H_2O, 40mL/min.). The fractions containing the desired compound were combined, evaporated, and dried under reduced pressure to give 3-{2-[((2S)-5-amino-2-{[(4-biphenylylamino)carbonyl]amino}pentanoyl)-amino]phenyl}acrylic acid (105mg).

A mixture of the above 3-{2-[((2S)-5-amino-2-{[(4-biphenylylamino)carbonyl]amino}pentanoyl)-amino]phenyl}acrylic acid (95mg, 0.20mmol) and 10% palladium on carbon (50% wet, 10mg) in MeOH (5mL) was hydrogenated at atmospheric pressure of hydrogen at room temperature. After 4 hours, the catalyst was removed by filtration and evaporated to give residue, which was dissolved in DCM (20mL). To the resulting mixture was added 1-(benzyloxycarbonyloxy)-benzotriazole-6-carboxamidomethyl polystyrene (1.08g, 0.93mmole/g), and the mixture was shaken for 1 week at room temperature. The resin was removed by filtration and evaporation of the solvent gave a residue, which was purified by HPLC (reverse phase C_{18}, 5μ, 30mm×50mm column, 254nm, gradient 10-90% 0.1% TFA in CH_3CN / 0.1% TFA in H_2O, 40mL/min.). The fractions containing the target compound were combined, evaporated, and dried under reduced pressure to give the target compound (12.4mg).

MS ((-)ESI) m/z : 607 $(M-H)^-$.

^{1}H-NMR (DMSO-d_6) : δ 1.45-2.05(4H, m), 2.40-2.55(2H, m), 2.81(2H, t, J=7.5Hz), 3.00-3.15(2H, m), 4.40-4.60(1H, m), 5.00(2H, s), 6.55(1H, d, J=7.6Hz),

7.10-7.65(19H, m), 8.81(1H, s), 9.63(1H, S), 12.17(1H, br-s).

In order to illustrate the usefulness of the object Compound (I), the pharmacological test is carried out as shown in the following.

Test Example

Binding assay using membrane preparation with the expression of prostanoid receptor subtype

[I] Test Compound:

Sodium 6-{(2S)-2-[(1-benzofuran-2-yl-carbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino}-hexanoate (Example 23)

[II] Test Method:

The membrane fraction was prepared using COS-7 cells transfected prostanoid receptor subtype (human EP4).

The standard assay mixture contained membrane fraction, [^{3}H]-PGE_2 in final volume of 0.25mL was incubated for 1hour at 30℃. The reaction was terminated by that the mixture was rapidly filtered through a glass filter (GF/B). Then the filter was washed with 4mL of ice-cooled buffer two times. The radioactivity associated with the filter was measured by liquid scintillation counting.

In the experiment for competition of specific [^{3}H]-PGE_2 was added at a concentration of 10nM. The following buffer was used in all reactions.

Buffer: 20mM Mes (pH 6.0), 1mM EDTA, 10mM $MgCl_2$

The inhibition (%) of the compound at a concentration of 10nM was shown below.

[III] Test Result:

The test compound (1.0×10^{-8}M) showed the inhibition of 80% or more.

It appeared, from the above-mentioned inhibition test, that Compound (I) or pharmaceutically acceptable salt thereof of the present invention binds to PGE_2 receptor subtype, especially EP4, preferentially more than PGE_2. Therefore, Compound (I) of the present invention has an activating or inhibiting activity of PGE_2 receptor subtype.

In consequence, Compound (I) or pharmaceutically acceptable salt thereof is useful for treating or preventing diseases mediated by PGE_2, more particularly useful for treating or preventing kidney dysfunction (e.g., acute nephritic syndrome, recurrent or persistent hematuria, chronic nephritic syndrome, nephritic syndrome, rapidly progressive nephritic syndrome, acute renal failure, chronic renal failure), inflammation and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis), inflammatory eye condition (e.g., conjunctivitis), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung), condition of the gastrointestinal tract associated with inflammation (e.g., aphthous ulcer, Chrohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome), gingivitis, inflammation, nephrithis, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus

erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjgren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (e.g., diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis, contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, migraine, liver dysfunction (e.g., hepatitis, cirrhosis), gastrointestinal dysfunction (e.g., diarrhea, inflammatory bowel diseases), shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia cancer, cancer cachexia, breast cancer, calculosis, lithiasis (especially, urolithiasis), solid caricinoma, neurodegenerative disorder, sleeping disorder, hyperaldosteronism sexual dysfunction, or the like in human being or animal.

The Compound (I) of the present invention or its salts is also useful for the preparation of medicament having diuretic activity, which are useful for the preparation of drugs indicated treating or preventing various edema (e.g. cardiac edema, cerebral edema), hypertension such as malignant hypertension or the like, premenstrual tension, urinary calculus, oliguria such as the one caused by acute or chronic failure, hyperphosphaturia, or the like.